Rev Esp Cardiol. 2022;75(12):1050–1058

Review article

Environment and cardiovascular health: causes, consequences and opportunities in prevention and treatment

Jordi Bañeras,[a,b] Josep Iglesies-Grau,[c] María Téllez-Plaza,[d] Vicente Arrarte,[e] Néstor Báez-Ferrer,[f] Begoña Benito,[a,b] Raquel Campuzano Ruiz,[g] Alberto Cecconi,[h] Alberto Domínguez-Rodríguez,[b,f] Antonio Rodríguez-Sinovas,[a,b] Francisco Ujueta,[i] Carlos Vozzi,[j] Gervasio A. Lamas,[i,k] and Ana Navas-Acién[l,*]

[a] *Servei de Cardiologia, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca, Universitat Autònoma de Barcelona, Barcelona, Spain*
[b] *Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain*
[c] *Centre ÉPIC and Research Center, Montreal Heart Institute, Montreal, Quebec, Canada*
[d] *Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid, Spain*
[e] *Servicio de Cardiología, Hospital General Universitario Dr. Balmis, ISABIAL, Alicante, Spain*
[f] *Servicio de Cardiología, Hospital Universitario de Canarias, Universidad Europea de Canarias, Santa Cruz de Tenerife, Spain*
[g] *Servicio de Cardiología, Hospital Universitario Fundación de Alcorcón, Alcorcón, Madrid, Spain*
[h] *Servicio de Cardiología, Hospital Universitario de La Princesa, Madrid, Spain*
[i] *Columbia University Division of Cardiology, Mount Sinai Medical Center, Miami Beach, Florida, United States*
[j] *Departamento de Cardiología, Instituto Vozzi, Rosario, Argentina*
[k] *Department of Medicine, Mount Sinai Medical Center, Miami Beach, Florida, United States*
[l] *Department of Environmental Health Sciences, Columbia University Mailman School of Public Health, Nueva York, United States*

Article history:
Received 2 May 2022
Accepted 4 May 2022
Available online 2 August 2022

Keywords:
Environmental cardiology
Air pollution
Particulate matter
Environment
Metals

ABSTRACT

The environment is a strong determinant of cardiovascular health. Environmental cardiology studies the contribution of environmental exposures with the aim of minimizing the harmful influences of pollution and promoting cardiovascular health through specific preventive or therapeutic strategies. The present review focuses on particulate matter and metals, which are the pollutants with the strongest level of scientific evidence, and includes possible interventions. Legislation, mitigation and control of pollutants in air, water and food, as well as environmental policies for heart-healthy spaces, are key measures for cardiovascular health. Individual strategies include the chelation of divalent metals such as lead and cadmium, metals that can only be removed from the body via chelation. The TACT (Trial to Assess Chelation Therapy, NCT00044213) clinical trial demonstrated cardiovascular benefit in patients with a previous myocardial infarction, especially in those with diabetes. Currently, the TACT2 trial (NCT02733185) is replicating the TACT results in people with diabetes. Data from the United States and Argentina have also shown the potential usefulness of chelation in severe peripheral arterial disease. More research and action in environmental cardiology could substantially help to improve the prevention and treatment of cardiovascular disease.

Medioambiente y salud cardiovascular: causas, consecuencias y oportunidades en prevención y tratamiento

Palabras clave:
Cardiología ambiental
Contaminación atmosférica
Material particulado
Medioambiente
Metales

RESUMEN

El medioambiente es un gran determinante de la salud cardiovascular. La cardiología ambiental estudia la contribución de las exposiciones ambientales con el objetivo de minimizar las influencias nocivas de la contaminación y promover la salud cardiovascular mediante estrategias preventivas o terapéuticas específicas. La presente revisión se centra en el material particulado y los metales, contaminantes con la evidencia científica más sólida, e incluye las posibles intervenciones. La legislación, la mitigación y el control de los contaminantes en el aire, el agua y los alimentos y las políticas ambientales de espacios cardiosaludables son medidas clave para la salud cardiovascular. Entre las estrategias individuales, cabe

* Corresponding author:.
E-mail address: an2737@cumc.columbia.edu (A. Navas-Acién).

https://doi.org/10.1016/j.rec.2022.05.030
1885-5857/

reseñar la quelación de metales divalentes como el plomo y el cadmio, que solamente pueden eliminarse del cuerpo vía quelación. El ensayo clínico TACT (NCT00044213) demostró el beneficio cardiovascular en pacientes con un infarto de miocardio previo, especialmente en los diabéticos. Actualmente, el ensayo TACT2 (NCT02733185) está reproduciendo los resultados del TACT en personas con diabetes. Datos de Estados Unidos y Argentina también han mostrado la posible utilidad de la quelación en la enfermedad arterial periférica grave. Más investigación y acción en cardiología ambiental podría contribuir sustancialmente a mejorar la prevención y el tratamiento de las enfermedades cardiovasculares.

Abbreviations

CVD: cardiovascular disease
MI: myocardial infarction
PM: particulate matter

CONCEPT OF ENVIRONMENTAL CARDIOLOGY

Cardiovascular diseases (CVD) are a leading cause of hospitalization and death in most parts of the world and develop as the result of complex interactions between genes and the environment. The undeniable gap between the incidence of CVD and the identification of risk factors has led the scientific community to investigate additional risk factors, particularly modifiable factors such as those related to the environment.[1–13]

In the 20th century, short- and long-term effects due to air pollution were seen to produce notable increases in cardiovascular morbidity and mortality.[14–17] The systematic analysis of the increase in cardiovascular morbidity and mortality coinciding with increased air pollution in a number of US cities,[18,19] as well as evidence showing a link between metals such as mercury and the risk of myocardial infarction (MI)[20] or between lead and cardiovascular mortality,[21] led to the concept of "environmental cardiology" in the early 2000s in an article published in *Environmental Health Perspectives*, an influential journal in the field of environmental health science.[4]

Epidemiologic studies have shown a steady increase in the risk of CVD linked to short- and long-term exposure to concentrations of polluting particulates in the environment, with the cardiovascular system most commonly affected.[2,4,8,22] Several plausible physiologic and pathologic pathways have been described, for instance, increased coagulation, thrombosis, predisposition toward arrythmia, acute arterial vasoconstriction, systemic inflammatory responses, and the chronic influence of atherosclerosis.[1,10,11,23–42] These effects have been linked to ischemic heart disease, congestive heart failure, MI, malignant ventricular arrhythmia, plaque vulnerability, acute thrombosis, stroke, diabetes mellitus, and hypertension.[5,8,9,43–45] In this context, the largest study on the influence of the global disease burden showed that air pollution is the fourth most important risk factor after hypertension, tobacco use, and dietary factors, even ahead of hypercholesterolemia.[3] Among the 6.7 million deaths attributable to environmental pollution in 2019, 50% were due to CVD.[3] At an individual level, people around the world would lose an average of 1.7 years of life as a result of exposure to anthropogenic air pollution, and sources not readily preventable (eg, desert dust or natural fires) are included, then the loss would rise to 2.9 years.[46]

What is environmental cardiology?

Exposure to environmental pollution—which includes chemical substances such as particulate matter with an aerodynamic diameter $\leq$ 2.5 μm (PM2.5), metals and some organic compounds, and noise pollution—contributes to the risk of CVD. In the absence of a universal definition, we suggest defining environmental cardiology as the interdisciplinary science that studies the contribution of environmental exposure to CVD, with the aim of developing specific preventive or therapeutic strategies to minimize the harmful influence of environmental pollution and to promote cardiovascular health. This review focuses on PM and metals, the pollutants with the most sound scientific evidence.

CLINICAL EVIDENCE

Environmental pollution

What are the effects of pollution on our health? The clinical events associated with environmental pollution have been thoroughly described in the literature.[2,7] However, there does not seem to be a minimum safety threshold, and the relationship may even be supralinear, ie, the adverse effects of pollution changes at lower exposure levels are worse than when the same changes occur at higher exposure levels.[47,48]

Air pollution is associated with increased hospitalizations due to ischemic cardiac disease, atrial fibrillation, and heart failure[2] but has also been linked with hospitalization due to aortic dissection[43] and with the development of congenital heart disease.[49] Some data also link air pollution to peripheral artery disease, as summarized in a recent report from the American Heart Association.[50] The proinflammatory state produced by environmental pollution contributes to a poorer prognosis in CVD patients.[45,51]

Exposure to higher air pollution increases mortality.[8,17,18,21,45,47] Although it has been traditionally presumed to result in cardiovascular mortality regardless of pollutant composition,[23] recent data show that metal- and acid-rich particles are more toxic.[52] The increase in daily CVD mortality seen with an increase of 10 $\mu g/m^3$ in the 2-day average PM2.5 was 0.55%.[53] Even exposure to PM from desert dust has been associated with an increased cardiovascular mortality, both on the day of exposure and on the previous day.[54]

In actuality, PM is a mix of substances of varying toxicity and can include soot, hydrocarbons, sulfur and nitrogen compounds, dust, and various metals such as arsenic, cadmium, and nickel. Many pollutants form particles suspended in the air and can be inhaled. These particles may come from natural sources (forest fires, sea spray, volcanic eruptions, desert dust) or from human sources (industrial activity, transportation, heating systems, and

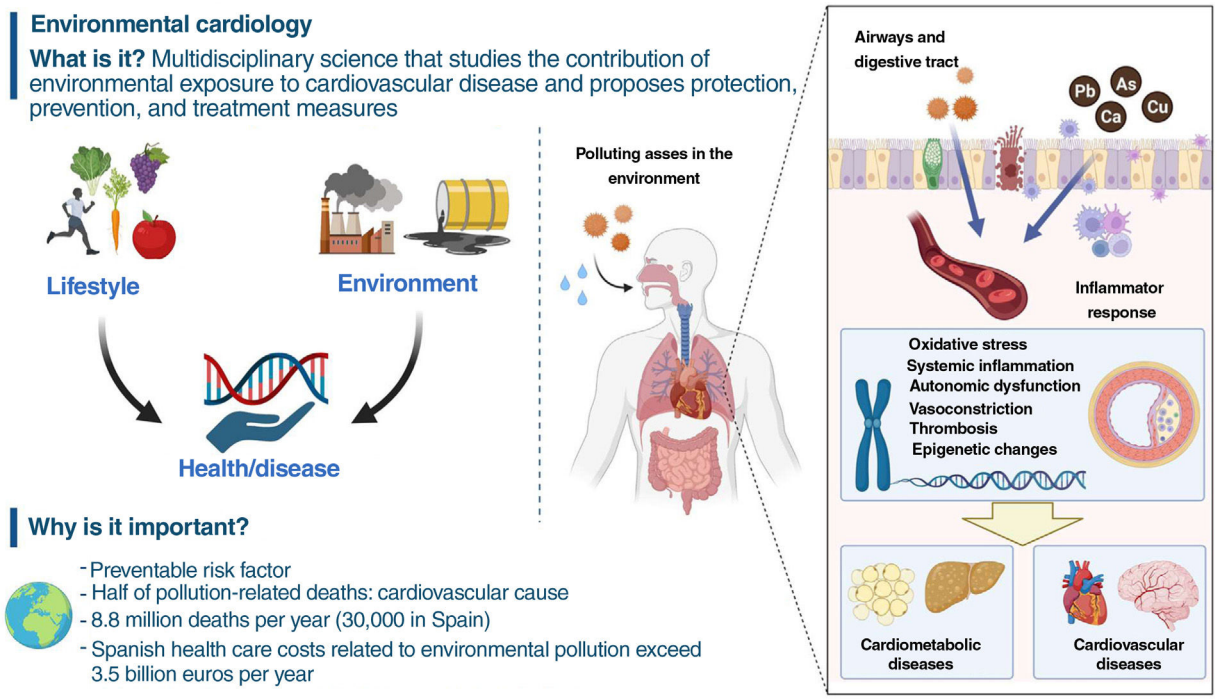

Figure 1. Central illustration. Definition and importance of environmental cardiology.

fossil fuel combustion in general) and are classified according to size, an important factor in their harmful effects.

Particulate with a diameter between >2.5 and ≤ 10 μm is considered coarse and is deposited in the upper airways. Fine particulate (PM2.5) is deposited in deeper areas of the lungs, from where they enter the bloodstream. They are usually produced by human activities such as woodburning, industry, construction, automobiles, and the transportation sector in general (figure 1). Other sources are forest fires, household dust, and cigarette and kitchen smoke. Ultrafine particulate (diameter ≤ 0.1 μm [PM0.1]) is also given off by vehicles, particularly diesel-powered engines, and readily enters the systemic circulation. Fossil fuels burned for heating and cooking also generate ultrafine particulate.

Heavy metals

A growing number of epidemiologic studies, supported by experimental evidence and toxicologic studies, indicates that metal exposure increases the risk of CVD. A recent US study with over 9000 individuals showed that participants with high exposure to heavy metals (lead and cadmium) had CVD-related mortality that was 1.63-fold that of participants with low exposure.[55] The Strong Heart Study,[56] a cohort study with 3600 participants from populations of native Americans who had been exposed to arsenic in their drinking water, observed higher cardiovascular and all-cause mortality (hazard ratio = 1.28 per increase in interquartile interval of arsenic in urine). In this study, greater exposure to cadmium was also associated with a higher risk of cardiovascular morbidity and mortality due to ischemic heart conditions, heart failure, and cerebrovascular disease.[57]

Environmental metals are ubiquitous, and populations are chronically exposed through food, air, tobacco smoke, and even drinking water in some areas. Therefore, the potential impact of this exposure on public health is considerable. In the United States, 32% of the decrease in cardiovascular mortality rates observed between 1988 and 2004 was explained by reduced exposure to lead and cadmium, adjusting for traditional risk factors.[58]

Several studies in Spanish populations have shown a relationship between metal biomarkers and various outcomes related to cardiovascular risk.[9,44,59,60] The Hortega Study[9,12] looked at a sample of the general population in Valladolid (Spain), finding that copper, zinc, antimony, cadmium, chromium, and vanadium concentrations were associated with the incidence of CVD over a 13-year of follow-up. In the Aragon workers' health study (AWHS cohort),[61] workers with urine metal concentrations similar to those seen in the study by Hortega et al., high urine concentrations of inorganic arsenic, cadmium, titanium, and perhaps antimony were linked with varying degrees of subclinical atherosclerosis.[41]

The AWHS cohort study is particularly interesting, given that earlier studies usually focused only on the carotid arteries rather than vascular territories such as the femoral and coronary territories. In a Bangladeshi study[62] and in the Strong Heart Study,[63] arsenic exposure has been associated with an increased thickness of the intima-media layers of the carotid. A direct association has also been found between blood cadmium concentrations and the thickness of the intima-media layers of the carotid of Austrian women,[11] and the prevalence of atherosclerotic plaque in a Swedish study.[10,42] In the AWHS study, arsenic and cadmium were linked to the presence of carotid plaque, but cadmium and titanium were also linked to femoral plaque, and titanium and possibly cadmium and antimony were linked to coronary calcium. These associations persisted after adjusting for other metals and for classic risk factors.[61]

Metal levels could aid early screening for individuals at risk due to exposure, thus allowing individualized measures to be taken before clinical events occur. A randomized clinical trial evaluating the administration of a heavy-metal chelator agent known as disodium ethylenediaminetetraacetic acid (EDTA) vs placebo in patients with a prior MI showed an improvement in the combined primary outcome (time to all-cause death, recurrent MI, coronary revascularization, hospitalization due to angina or stroke) in the intervention group (hazard ratio = 0.82).[64] The subgroup of diabetic patients had even greater benefits and has a risk reduction of 41%.[65]

EVIDENCE FROM MECHANISTIC STUDIES

Air pollution enters the body through the alveoli and promotes the development of CVD through the activation of various mechanisms, such as inflammation, endothelial dysfunction, oxidative stress, autonomic dysfunction, and thrombogenicity.[8] Other pollutants can enter the gastrointestinal system through water or other drinks.

Increased inflammation is associated with ischemic events, arrythmia, heart failure, and a lack of control of cardiovascular risk factors. Air pollution promotes the production of interleukin 6 (IL-6) and C-reactive protein, inflammatory markers associated with a higher risk of CVD.[24] Exposure to greater environmental pollution in the 24 hours prior to hospitalization modulates the inflammatory profile of patients with MI. Greater acute exposure to sulfur dioxide, a gas linked to fossil fuel combustion and industrial activity, has been associated with larger MIs and stronger white blood cell activity.[25]

Chronic exposure to high air pollution has been associated with the formation and vulnerability of coronary plaque at values far below European Union limits (annual PM2.5 $< 25\ \mu g/m^3$). Optical coherence tomography showed a higher prevalence of thin-cap fibroatheroma and macrophagic infiltrates in patients with acute coronary syndrome exposed to a higher annual PM2.5.[26] Even within the exposure limits recommended by the World Health Organization (WHO) before 2021 (annual PM2.5 $< 10\ \mu g/m^3$, currently annual PM2.5 $< 5\ \mu g/m^3$), the highest levels are associated with great arterial white blood cell activity and leukopoietic activity measured by ^{18}F-FDG uptake, activity levels associated with cardiovascular events during patient follow-up.[27]

Oxidative stress also plays a key role in the pathogenic vascular and myocardial effects of environmental pollution.[28] Epidemiologic and controlled-exposure studies have observed positive associations between PM2.5 concentrations and concentrations of several plasma and urine biomarkers for oxidative stress,[29] including increases in thiobarbituric acid reactive substances (TBARS), a marker of lipid peroxidation.[30] The role of oxidative stress in endothelial damage is supported by data from animal models. Controlled, short-term exposure to diesel exhaust at concentrations similar to those detected in urban environments produces transitory microcirculation dysfunction.[32] The inhalation of diesel particulate causes endothelial dysfunction in rats, an effect that can be reverted using a treatment with oxygen free radical scavengers.[33] Oxidative stress also has a prominent role on the myocardium. Isolated rat cardiomyocytes exposed to diesel particulate exhibited lower contractility, which was attenuated with antioxidants.[34] In another rodent experiment, exposure to diesel particulate increased susceptibility to myocardial damage induced by ischemia-reperfusion, an effect associated with the local generation of oxygen free radicals and proinflammatory cytokines.[35] In rats, prolonged PM2.5 exposure causes damage to myocardial cells with ultrastructural and inflammatory infiltrate changes[36] and mitochondrial abnormalities,[37] leading to remodeling and hypertrophy.[38]

Several environmental pollutants (eg, lead) can cause autonomic dysfunction and can trigger reflex arcs that affect heart rate and promote arrhythmia.[39] Most epidemiologic studies have described adverse associations between various indices of heart rate variability and the concentrations of PM2.5 and other pollutants,[40] which may be related to the higher incidence of arrythmia reported in patients with MI.[45] Additionally, calcium/calmodulin-dependent protein kinase II (CaMKII) has been possibly implicated in these proarrhythmic effects.[66] These mechanisms are also involved in the vascular toxicity of metals such as cadmium and lead.[67] For instance, lead can substitute for calcium in calmodulin. This mechanism has been linked to the synthase regulation of nitric oxide, affecting the production of nitric oxide, key for endothelial function and for the inhibition of platelet aggregation.[68]

Both PM and the gaseous components of air pollution also favor the appearance of thrombi.[69] Available evidence indicates that acute exposure to PM2.5 shifts the hemostatic balance toward a prothrombotic state. This state has been associated with elevated oxidative stress and inflammation biomarkers, as well as with platelet activation and fibrinolysis reductions.[69] Furthermore, exposure to ultrafine particulate increases the *in vitro* formation of factor XIIa, whereas postexposure thrombin formation is inhibited in animals deficient in this factor, indicating direct modulation of the intrinsic coagulation pathway.[70]

Numerous studies have linked metal exposure with biomarkers of oxidative stress[67,71] and metabolic[72] and epigenetic patterns.[73,74] Gene-environment interactions are another field of growing interest, as they could aid early screening for individuals who may benefit from stronger prevention strategies and could identify biological mechanisms to help understand the role of the environment in CVD and broaden the strategies used to prevent and monitor these diseases.

PREVENTION STRATEGIES AND TREATMENT

First of all, what can be done? Public health measures, through legislation and mitigation measures and control of environmental pollutants, are key strategies to minimize air and water pollution as well as food contamination with toxic compounds and to protect populations from the harmful effects of these substances on cardiovascular health (figure 2). To encourage such measures, in September 2021 the WHO published new air quality guidelines, recommending that countries establish a PM2.5 annual limit of $5\ \mu g/m^3$ and a daily limit of $15\ \mu g/m^3$. These guidelines are well below the legally established limits in the European Union, the United States, and most other countries. In Spain and many Latin American countries, most cities have pollution levels far above the WHO guidelines and even above the limits established by the countries themselves. As a collective strategy, therefore, legislation should be proposed and enacted to comply with WHO recommendations. Environmental policies that reduce pollution levels around the world are, for instance, the optimal design of bicycle lanes and pedestrian spaces, the promotion of public transportation, measures to reduce emissions from fuel and other toxic gases, and new building codes for sustainable housing and offices, the prohibition and elimination of old, highly-polluting heating systems, and the promotion of green areas.

Individual protection strategies (figure 2) could include respiratory barriers as an option for outdoor environments. Nevertheless, respiratory protection such as gauze, cotton, surgical, or cloth masks has not yet been validated for reducing exposure to PM2.5, hence they are not recommended in this

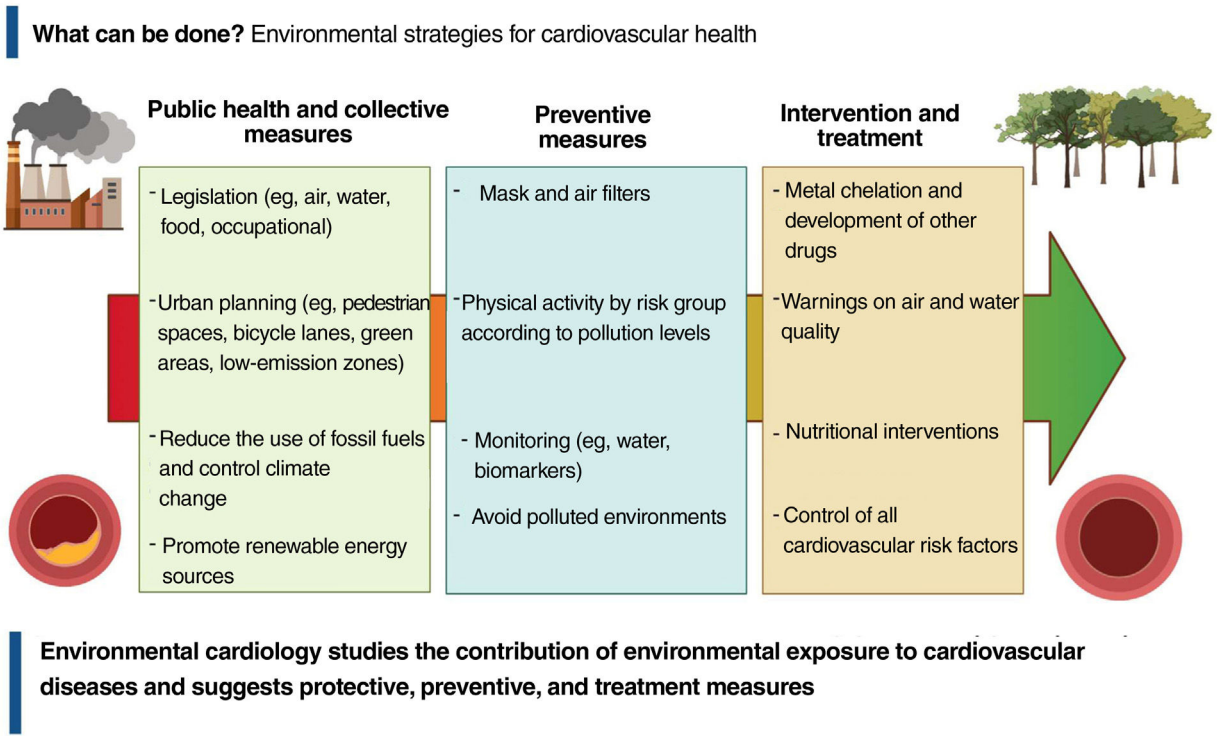

Figure 2. Environmental strategies for cardiovascular health.

regard. Other types of personal protective equipment, such as face masks with respirators (eg, N95 masks), are specifically designed and validated to filter 95% of particles, including PM2.5. However, no personalized intervention intended to reduce pollution exposure has been shown to reduce cardiovascular events.[22] More studies would be needed to assess the effectiveness of these kinds of personal barriers.

Indoors, PM2.5 concentrations can be reduced with high-efficiency air purification systems in home air conditioning installations. Although these systems has been reported to have an impact in lowering inflammatory and circulatory thrombogenic biomarkers and blood pressure,[75] the evidence is insufficient, discouraging statements on the cardiovascular benefits of air purifiers.[76] Additionally, real-time information on air pollution levels could be a way to protect public health under certain circumstances.[77] However, there is not enough evidence on the clinical impact of this measure and on who may benefit.

Diet may also have an impact on the effect of environmental pollution on our health. Dietary supplements with omega-3 fatty acids have been associated with short-term subclinical cardiovascular benefits against PM2.5 exposure,[78] and supplements with vitamin B (folic acid, B_6, B_{12}) have shown a possible benefit in mitigating the effects of PM2.5 on inflammation and autonomic cardiac dysfunction in pilot studies.[79] Folic acid supplements have also shown an ability to eliminate arsenic from the body more quickly and to reduce its toxicity.[80]

Regarding physical exercise in areas with high environmental pollution, the interaction depends on multiple mechanisms. Public health models have estimated that in most cases, the benefits of physical exercise outweigh the risks from pollution,[81] although evidence is insufficient for people with established risk factors of CVD.[82]

Research on treatments has focused on eliminating metals from the body. Cadmium and lead, which are divalent cations, can be treated with high-affinity chelators, such as EDTA and its salts (disodium EDTA and calcium disodium EDTA). To date, several studies[83–85] have shown that intravenous disodium EDTA enhances the urinary excretion of toxic metals, including cadmium and lead. Arenas et al.[83] published the results of disodium EDTA infusion in patients with a history of MI, which produced a 71% increase in total urinary excretion of metals compared with original levels, with a notable effect on lead (3.835% increase) and cadmium (633% increase). High excretion of these metals after EDTA administration is indicative of the cumulative exposure to these metals over the years from various sources (air pollution, water, tobacco, soil and food contamination, etc.) and of the difficulty in eliminating these toxic metals, highly similar to essential metals such as calcium and zinc, which they replace in many proteins and enzymes.

The Trial to Assess Chelation Therapy (TACT) is a double-blind, placebo-controlled, 2×2 factorial clinical trial to evaluate the risks and benefits of 40 disodium EDTA infusions compared with placebo in 1708 participants with a history of MI. Patients received follow-up for 5 years. The trial showed a significant reduction of 18% ($P = .035$) of the composite main outcome of death, MI, stroke, coronary revascularization, and hospitalization for angina.[64] The most obvious benefit was seen in patients with a history of diabetes, with a 41% reduction in the hazard ratio of the combined cardiovascular endpoint ($P < .001$) and a 43% reduction in all-cause mortality ($P = .011$).[65] At present, the TACT2 clinical trial (NCT02733185) is reproducing the TACT results in people with diabetes. The results from TACT2 will be available by late 2023. In a recent meta-analysis, the patients most clearly benefitting from EDTA treatment were those with

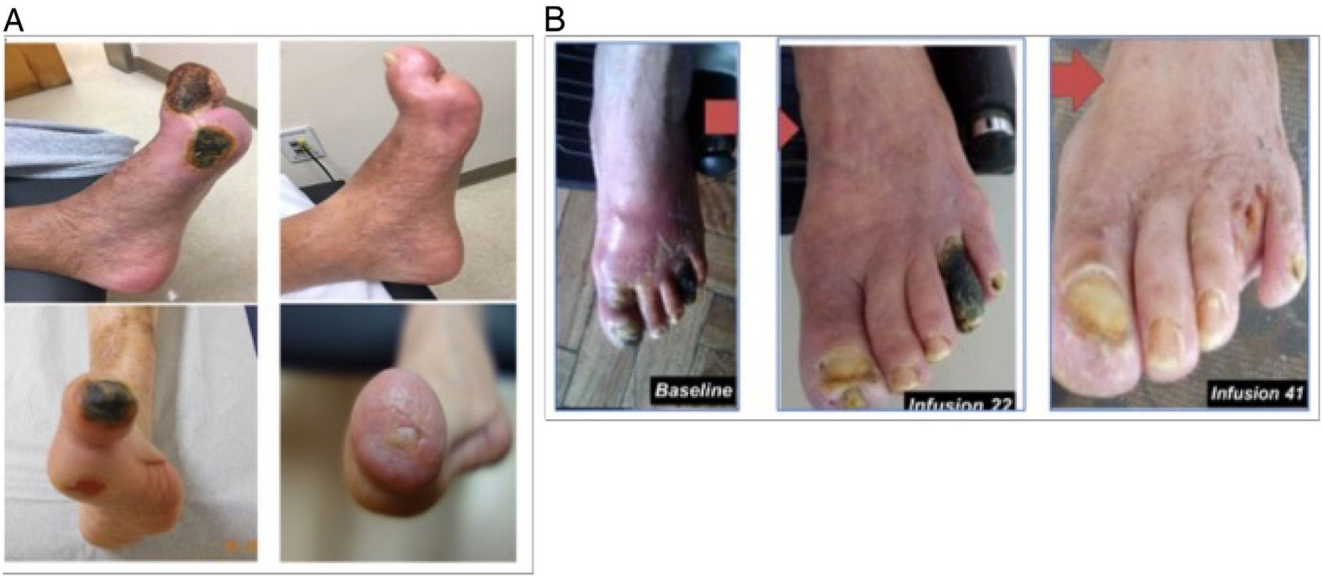

Figure 3. Photographs of patients with severe peripheral artery disease at the beginning and after repeated infusions of disodium EDTA (ethylenediaminetetraacetic acid) chelator in a patient in Miami, United States (A, reproduced with permission from Arenas et al.[87]) and Rosario, Argentina (B, reproduced with permission from Ujueta et al.[88]).

Table 1
Metal biomarkers associated with cardiovascular disease.

Metal	Sample	Half-life	Method	Additional Information	Possible Reference Range*
Arsenic	Urine	1 to 30 d depending on species	Liquid chromatography–mass spectrometry for species separation	Avoid eating fish on the days prior to collecting the sample	10 μg/L (first morning urine)
Cadmium	Blood Urine	30 to 100 d Decades	Mass spectrometry (blood and urine)	Smokers have high values	1 μg/L 1 μg/L (first morning urine)
Lead	Blood Bone	30 to 100 d Decades	Mass spectrometry (blood) X-ray fluorescence (bone)	Blood is the usual marker, whereas bone is used for research purposes	3.5 μg/dL (blood)

* For arsenic, urine concentration according to correspondence with the water limit; for cadmium, values around 3-fold the geometric mean in blood and urine from the National Health and Nutrition Examination Survey (NHANES),[55] clearly related to the toxicity level; blood lead concentration is based on the guidance from the Centers for Disease Control and Prevention for children and pregnant women, figures clearly associated with cardiovascular disease.

diabetes and peripheral artery disease.[86] Indeed, several cases have been published showing remarkable benefits in patients with severe peripheral artery disease in the United States[87] and Argentina[88] (figure 3). In the future, metal chelators that can be taken orally or are easier to administer may be developed. For instance, an oral chelator, known as succimer or dimercaptosuccinic acid (DMSA) and mainly used to treat saturnism (lead poisoning), is now available but has still not been tested for potential cardiovascular benefits.

A common question is whether it might be useful to measure metals in blood or urine to identify individuals at risk of CVD and to apply early intervention, and to determine the concentrations that could be considered toxic. There are several well-established metal biomarkers, with half-lives and sample types (blood, urine, others) considered most suitable for each metal (table 1). However, additional studies are needed to determine whether routine concentration testing could be helpful in clinical practice.

TRAINING AND SOCIOECONOMIC IMPACT

The residual risk is supported by ever-increasing evidence and probably includes uncontrolled risk factors as well as risk factors not considered or not yet known. Environmental pollution, although one of the cardiovascular risk factors,[3,11,12,46] has not yet achieved widespread health care and social awareness compared with other risk factors. Training in this field is greatly lacking in cardiology and, therefore, the effect of environment should be taught in training curricula, eg, as part of the curriculum on climate change and environmental health.

For the first time, the 2021 European Prevention Guidelines include a specific section on environmental pollution and classify air pollution reduction as class I, recommending lowering PM emissions and gaseous pollutants, reducing fossil fuel use, and limiting carbon dioxide emissions as measures to lower morbidity and mortality due to CVD.[89] Consequently, the European Commission agreed on a series of measures to be implemented

by 2030 to reduce harmful emissions from traffic, power plants, and agriculture, within the context of fighting climate change.

Patients at risk for CVD should be advised to avoid long-term exposure to areas with high environmental pollution. Opportunistic risk screening programs (class IIb recommendation, level of evidence C) may be considered.[89] In addition, according to the same guidelines, patient and health care professional organizations are essential for training and political initiatives. "Clean air" legislation should be strengthened to encourage lower particulate emissions and the use of public transportation. Learning about the impact of environmental pollution should start in schools and families. Patient training (eg, patient schools) could also be fostered.

Last, environmental pollution also has a financial impact. Air pollution-related mortality represents a cost to the global economy of around US$225 billion dollars in lost wages and over US$5 trillion in welfare losses.[90] Problems derived from air pollution cost every person living in Spain nearly 1000 euros each year.[91]

FUNDING

The authors declare the following sources of funding: A. Navas-Acién from the National Institutes of Health (P42ES033719, P30ES009089); J. Bañeras, B. Benito, and A. Rodríguez Sinovas from the Instituto de Salud Carlos III (ISCIII) (PI20/01649 and CIBERCV), co-funded by the European Regional Development Fund (ERDF-FEDER, a way to build Europe); A. Domínguez Rodríguez and N. Báez-Ferrer of the Instituto de Salud Carlos III (ISCIII) (PI21/00404), co-funded by the European Regional Development Fund (ERDF-FEDER, a way to build Europe). J. Iglesies-Grau, M. Téllez-Plaza, V. Arrarte, R. Campuzano Ruiz, A. Cecconi, Francisco Ujueta, C. Vozzi, and G.A. Lama have no sources of funding related to this article.

AUTHORS' CONTRIBUTIONS

All authors contributed to the writing and critical review of this article.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Bhatnagar A. Environmental cardiology: studying mechanistic links between pollution and heart disease. *Circ Res.* 2006;99:692–705.
2. Brauer M, Casadei B, Harrington RA, et al. WHF Air Pollution Expert Group. Taking a Stand Against Air Pollution-The Impact on Cardiovascular Disease: A Joint Opinion From the World Heart Federation, American College of Cardiology, American Heart Association, and the European Society of Cardiology. *Circulation.* 2021;143:e800–e804.
3. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396:1204-1222.
4. Weinhold B. Environmental cardiology: getting to the heart of the matter. *Environ Health Perspect.* 2004;112:A880–A887.
5. Brook RD, Franklin B, Cascio W, et al. Expert Panel on Population and Prevention Science of the American Heart Association. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation.* 2004;109:2655–2671.
6. Newman JD, Bhatt DL, Rajagopalan S, et al. Cardiopulmonary Impact of Particulate Air Pollution in High-Risk Populations: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020;76:2878–2894.
7. Newby DE, Mannucci PM, Tell GS, et al.ESC Working Group on Thrombosis, European Association for Cardiovascular Prevention and Rehabilitation; ESC Heart Failure Association. Expert position paper on air pollution and cardiovascular disease. *Eur Heart J.* 2015;36:83–93.
8. Rajagopalan S, Al-Kindi SG, Brook RD. Air Pollution and Cardiovascular Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2018;72:2054–2070.
9. Domingo-Relloso A, Grau-Perez M, Briongos-Figuero L, et al. The association of urine metals and metal mixtures with cardiovascular incidence in an adult population from Spain: the Hortega Follow-Up Study. *Int J Epidemiol.* 2019;48:1839–1849.
10. Fagerberg B, Barregard L, Sallsten G, et al. Cadmium exposure and atherosclerotic carotid plaques—Results from the Malmö diet and Cancer study. *Environ Res.* 2015;136:67–74.
11. Messner B, Knoflach M, Seubert A, et al. Cadmium is a novel and independent risk factor for early atherosclerosis mechanisms and in vivo relevance. *Arterioscler Thromb Vasc Biol.* 2009;29:1392–1398.
12. Tellez-Plaza M, Briongos-Figuero L, Pichler G, et al. Cohort profile: the Hortega Study for the evaluation of non-traditional risk factors of cardiometabolic and other chronic diseases in a general population from Spain. *BMJ Open.* 2019;9:e024073.
13. Lamas GA, Ujueta F, Navas-Acien A. Lead and cadmium as cardiovascular risk factors: the burden of proof has been met. *J Am Heart Assoc.* 2021;10:e018692.
14. Nemery B, Hoet PH, Nemmar A. The Meuse Valley fog of 1930: an air pollution disaster. *Lancet.* 2001;357:704–708.
15. Bell ML, Davis DL. Reassessment of the lethal London fog of 1952: Novel indicators of acute and chronic consequences of acute exposure to air pollution. *Environ Health Perspect.* 2001;109(Suppl 3):389–394.
16. Helfand WH, Lazarus J, Theerman P. Donora, Pennsylvania: An environmental disaster of the 20th century. *Am J Public Health.* 2001;91:553.
17. Dockery DW, Pope CA, 3rd. Xu X, et al. An association between air pollution and mortality in six U.S. cities. *N Engl J Med.* 1993;329:1753–1759.
18. Samet JM, Dominici F, Curriero FC, et al. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. *N Engl J Med.* 2000;343:1742–1749.
19. Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA.* 2006;295:1127–1134.
20. Guallar E, Sanz-Gallardo MI, van't Veer P, et al.Heavy Metals and Myocardial Infarction Study Group. Mercury, fish oils, and the risk of myocardial infarction. *N Engl J Med.* 2002;347:1747–1754.
21. Lustberg M, Silbergeld E. Blood lead levels and mortality. *Arch Intern Med.* 2002;162:2443–2449.
22. Rajagopalan S, Brauer M, Bhatnagar A, et al. American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and Stroke Council. Personal-Level Protective Actions Against Particulate Matter Air Pollution Exposure: A Scientific Statement From the American Heart Association. *Circulation.* 2020;142:e411–e431.
23. Hamanaka RB, Mutlu GM. Particulate Matter Air Pollution: Effects on the Cardiovascular System. *Front Endocrinol (Lausanne).* 2018;9:680.
24. Rückerl R, Greven S, Ljungman P, et al. Air pollution and inflammation (interleukin-6, C-reactive protein, fibrinogen) in myocardial infarction survivors. *Environ Health Perspect.* 2007;115:1072–1080.
25. Díaz-Chirón L, Negral L, Megido L, et al. Relationship Between Exposure to Sulphur Dioxide Air Pollution, White Cell Inflammatory Biomarkers and Enzymatic Infarct Size in Patients With ST-segment Elevation Acute Coronary Syndromes. *Eur Cardiol.* 2021;16:e50.
26. Montone RA, Camilli M, Russo M, et al. Air Pollution and Coronary Plaque Vulnerability and Instability: An Optical CoherenceTomography Study. *JACC Cardiovasc Imaging.* 2022;15:325–342.
27. Abohashem S, Osborne MT, Dar T, et al. A leucopoietic-arterial axis underlying the link between ambient air pollution and cardiovascular disease in humans. *Eur Heart J.* 2021;42:761–772.
28. Miller MR. Oxidative stress and the cardiovascular effects of air pollution. *Free Radic Biol Med.* 2020;151:69–87.
29. Li W, Wilker EH, Dorans KS, et al. Short-Term Exposure to Air Pollution and Biomarkers of Oxidative Stress: The Framingham Heart Study. *J Am Heart Assoc.* 2016;5:e002742.
30. Liu L, Ruddy T, Dalipaj M, et al. Effects of indoor, outdoor, and personal exposure to particulate air pollution on cardiovascular physiologym and systemic mediators in seniors. *Occup Environ Med.* 2009;51:1088–1098.
31. Mills NL, Törnqvist H, Gonzalez MC, et al. Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. *N Engl J Med.* 2007;357:1075–1082.
32. Mills NL, Törnqvist H, Robinson SD, et al. Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. *Circulation.* 2005;112:3930–3936.
33. Cherng TW, Paffett ML, Jackson-Weaver O, et al. Mechanisms of diesel-induced endothelial nitric oxide synthase dysfunction in coronary arterioles. *Environ Health Perspect.* 2011;119:98–103.
34. Gorr MW, Youtz DJ, Eichenseer CM, et al. In vitro particulate matter exposure causes direct and lung-mediated indirect effects on cardiomyocyte function. *Am J Physiol Heart Circ Physiol.* 2015;309:H53–H62.

35. Robertson S, Thomson AL, Carter R, et al. Pulmonary diesel particulate increases susceptibility to myocardial ischemia/reperfusion injury via activation of sensory TRPV1 and b1 adrenoreceptors. *Part Fibre Toxicol.* 2014;11:12.
36. Ma XN, Li RQ, Xie JL, et al. PM2.5-induced inflammation and myocardial cell injury in rats. *Eur Rev Med Pharmacol Sci.* 2021;25:6670–6677.
37. Daiber A, Kuntic M, Hahad O, et al. Effects of air pollution particles (ultrafine and fine particulate matter) on mitochondrial function and oxidative stress — Implications for cardiovascular and neurodegenerative diseases. *Arch Biochem Biophys.* 2020;696:108662.
38. Bai L, Zhao Y, Zhao L, et al. Ambient air PM(2.5) exposure induces heart injury and cardiac hypertrophy in rats through regulation of miR-208a/b, a/b-MHC, and GATA4. *Environ Toxicol Pharmacol.* 2021;85:103653.
39. Perez CM, Hazari MS, Farraj AK. Role of autonomic reflex arcs in cardiovascular responses to air pollution exposure. *Cardiovasc Toxicol.* 2015;15:69–78.
40. Buteau S, Goldberg MS. A structured review of panel studies used to investigate associations between ambient air pollution and heart rate variability. *Environ Res.* 2016;148:207–247.
41. Grau-Perez M, Caballero-Mateos MJ, Domingo-Relloso A, et al. Toxic Metals and Subclinical Atherosclerosis in Carotid, Femoral, and Coronary Vascular Territories: The Aragon Workers Health Study. *Arterioscler Thromb Vasc Biol.* 2022;42:87–99.
42. Fagerberg B, Bergström G, Borén J, et al. Cadmium exposure is accompanied by increased prevalence and future growth of atherosclerotic plaques in 64-year-old women. *J Intern Med.* 2012;272:601–610.
43. Chen J, Lv M, Yao W, et al. Association between fine particulate matter air pollution and acute aortic dissections: A time-series study in Shanghai, China. *Chemosphere.* 2020;243:125357.
44. Grau-Perez M, Navas-Acien A, Galan-Chilet I, et al. Arsenic exposure, diabetes-related genes and diabetes prevalence in a general population from Spain. *Environ Pollut.* 2018;235:948–955.
45. Bañeras J, Ferreira-Gonzalez I, Marsal JR, et al. Short-term exposure to air pollutants increases the risk of ST elevation myocardial infarction and of infarct-related ventricular arrhythmias and mortality. *Int J Cardiol.* 2018;250:35–42.
46. Lelieveld J, Pozzer A, Pöschl U, et al. Loss of life expectancy from air pollution compared to other risk factors: a worldwide perspective. *Cardiovasc Res.* 2020;116:1910–1917.
47. Di Q, Wang Y, Zanobetti A, et al. Air Pollution and Mortality in the Medicare Population. *N Engl J Med.* 2017;376:2513–2522.
48. Lanphear BP. Low-level toxicity of chemicals: No acceptable levels? *PLoS Biol.* 2017;15:e2003066.
49. Hu CY, Huang K, Fang Y, et al. Maternal air pollution exposure and congenital heart defects in offspring: A systematic review and meta-analysis. *Chemosphere.* 2020;253:126668.
50. Criqui MH, Matsushita K, Aboyans V, et al. American Heart Association Council on Epidemiology and Prevention; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; and Stroke Council. Lower Extremity Peripheral Artery Disease: Contemporary Epidemiology. *Management Gaps and Future Directions: A Scientific Statement From the American Heart Association Circulation.* 2021;144:e171–e191.
51. Cecconi A, Navarrete G, Garcia-Guimaraes M, et al. Influence of air pollutants on circulating inflammatory cells and microRNA expression in acute myocardial infarction. *Sci Rep.* 2022;12:5350.
52. Thurston GD, Chen LC, Campen M. Particle toxicity's role in air pollution. *Science.* 2022;375:506.
53. Liu C, Chen R, Sera F, et al. Ambient Particulate Air Pollution and Daily Mortality in 652 Cities. *N Engl J Med.* 2019;381:705–715.
54. Domínguez-Rodríguez A, Báez-Ferrer N, Abreu-González P, et al. Impact of Desert Dust Events on the Cardiovascular Disease: A Systematic Review and Meta-Analysis. *J Clin Med.* 2021;10:727.
55. Yao X, Steven Xu X, Yang Y, et al. Stratification of population in NHANES 2009-2014 based on exposure pattern of lead, cadmium, mercury, and arsenic and their association with cardiovascular, renal and respiratory outcomes. *Environ Int.* 2021;149:106410.
56. Kuo CC, Balakrishnan P, Gribble MO, et al. The association of arsenic exposure and arsenic metabolism with all-cause, cardiovascular and cancer mortality in the Strong Heart Study. *Environ Int.* 2022;159:107029.
57. Tellez-Plaza M, Guallar E, Howard BV, et al. Cadmium exposure and incident cardiovascular disease. *Epidemiology.* 2013;24:421–429.
58. Ruiz-Hernandez A, Navas-Acien A, Pastor-Barriuso R, et al. Declining exposures to lead and cadmium contribute to explaining the reduction of cardiovascular mortality in the US population, 1988-2004. *Int J Epidemiol.* 2017;46:1903–1912.
59. Galan-Chilet I, Grau-Perez M, De Marco G, et al. A gene-environment interaction analysis of plasma selenium with prevalent and incident diabetes: The Hortega study. *Redox Biol.* 2017;12:798–805.
60. Grau-Perez M, Pichler G, Galan-Chilet I, et al. Urine cadmium levels and albuminuria in a general population from Spain: A gene-environment interaction analysis. *Environ Int.* 2017;106:27–36.
61. Casasnovas JA, Alcaide V, Civeira F, et al. Aragon workers' health study—design and cohort description. *BMC Cardiovasc Disord.* 2012;12:45.
62. Chen Y, Wu F, Graziano JH, et al. Arsenic exposure from drinking water, arsenic methylation capacity, and carotid intima-media thickness in Bangladesh. *Am J Epidemiol.* 2013;178:372–381.
63. Mateen FJ, Grau-Perez M, Pollak JS, et al. Chronic arsenic exposure and risk of carotid artery disease: The Strong Heart Study. *Environ Res.* 2017;157:127–134.
64. Lamas GA, Goertz C, Boineau R, et al. *TACT Investigators Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: the TACT randomized trial JAMA.* 2013;309:1241–1250.
65. Escolar E, Lamas GA, Mark DB, et al. The effect of anEDTA-based chelation regimen on patients with diabetes mellitus and prior myocardial infarction in the Trial to Assess Chelation Therapy (TACT). *Circ Cardiovasc Qual Outcomes.* 2014;7:15–24.
66. Kim JB, Kim C, Choi E, et al. Particulate air pollution induces arrhythmia via oxidative stress and calcium calmodulin kinase II activation. *Toxicol Appl Pharmacol.* 2012;259:66–73.
67. Lamas GA, Ujueta F, Navas-Acien A. Lead and Cadmium as Cardiovascular Risk Factors: The Burden of Proof Has Been Met. *J Am Heart Assoc.* 2021;10:e018692.
68. Ujueta F, Navas-Acien A, Mann KK, et al. Low-Level Metal Contamination and Chelation in Cardiovascular Disease-A Ripe Area for Toxicology Research. *Toxicol Sci.* 2021;181:135–147.
69. Robertson S, Miller MR. Ambient air pollution and thrombosis. *Part Fibre Toxicol.* 2018;15:1.
70. Kilinç E, Van Oerle R, Borissoff JI, et al. Factor XII. activation is essential to sustain the procoagulant effects of particulate matter. *J Thromb Haemost.* 2011;9:1359–1367.
71. Domingo-Relloso A, Grau-Perez M, Galan-Chilet I, et al. Urinary metals and metal mixtures and oxidative stress biomarkers in an adult population from Spain: The Hortega Study. *Environ Int.* 2019;123:171–180.
72. Galvez-Fernandez M, Sanchez-Saez F, Domingo-Relloso A, et al. Gene-environment interaction analysis of redox-related metals and genetic variants with plasma metabolic patterns in a general population from Spain: The Hortega Study. *Redox Biol.* 2022;52:102314.
73. Domingo-Relloso A, Bozack A, Kiihl S, et al. Arsenic exposure and human blood DNA methylation and hydroxymethylation profiles in two diverse populations from Bangladesh and Spain. *Environ Res.* 2022;204(Pt B):112021.
74. Riffo-Campos AL, Fuentes-Trillo A, Tang WY, et al. *In silico* epigenetics of metal exposure and subclinical atherosclerosis in middle aged men: pilot results from the Aragon Workers Health Study. *Philos Trans R Soc Lond B Biol Sci.* 2018;373:20170084.
75. Chen R, Zhao A, Chen H, et al. Cardiopulmonary benefits of reducing indoor particles of outdoor origin: a randomized, double-blind crossover trial of air purifiers. *J Am Coll Cardiol.* 2015;65:2279–2287.
76. Xia X, Chan KH, Lam KBH, et al. Effectiveness of indoor air purification intervention in improving cardiovascular health: A systematic review and meta-analysis of randomized controlled trials. *Sci Total Environ.* 2021;789:147882.
77. Yoo G. Real-time information on air pollution and avoidance behavior: evidence from South Korea. *Popul Environ.* 2021;42:406–424.
78. Lin Z, Chen R, Jiang Y, et al. Cardiovascular Benefits of Fish-Oil Supplementation Against Fine Particulate Air Pollution in China. *J Am Coll Cardiol.* 2019;73:2076–2085.
79. Zhong J, Trevisi L, Urch B, et al. B-vitamin Supplementation Mitigates Effects of Fine Particles on Cardiac Autonomic Dysfunction and Inflammation: A Pilot Human Intervention Trial. *Sci Rep.* 2017;7:45322.
80. Bozack AK, Hall MN, Liu X, et al. Folic acid supplementation enhances arsenic methylation: results from a folic acid and creatine supplementation randomized controlled trial in Bangladesh. *Am J Clin Nutr.* 2019;109:380–391.
81. Tainio M, Jovanovic Andersen Z, Nieuwenhuijsen MJ, et al. Air pollution, physical activity and health: A mapping review of the evidence. *Environ Int.* 2021;147:105954.
82. Sinharay R, Gong J, Barratt B, et al. Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomised, crossover study. *Lancet.* 2018;391:339–349.
83. Arenas IA, Navas-Acien A, Ergui I, et al. Enhanced vasculotoxic metal excretion in post-myocardial infarction patients following a single edetate disodium-based infusion. *Environ Res.* 2017;158:443–449.
84. Alam ZH, Ujueta F, Arenas IA, et al.Urinary Metal Levels after Repeated Edetate Disodium Infusions: Preliminary. Findings. Int J. *Environ Res Public Health.* 2020;17:4684.
85. Petteruti S. Reduction of Lead Levels in Patients Following a Long-Term, Intermittent Calcium Ethylenediaminetetraacetic Acid (EDTA)-Based Intravenous Chelation Infusions: A Prospective Experimental Cohort. *Cureus.* 2020;12:e11685.
86. Ravalli F, Vela Parada X, Ujueta F, et al. Chelation Therapy in Patients With Cardiovascular Disease: A Systematic Review. *J Am Heart Assoc.* 2022;11:e024648.
87. Arenas I, Ujueta F, Diaz D, et al. Limb Preservation Using Edetate Disodium-based Chelation in Patients with Diabetes and Critical Limb Ischemia: An Open-label Pilot Study. *Cureus.* 2019;11:e6477.
88. Ujueta F, Vozzi C, Vozzi L, et al. Edetate Disodium-based Treatment in a Woman with Diabetes and Critical Limb Ischemia Scheduled for Lower Extremity Amputation. *Cureus.* 2019;11:e6142.
89. Visseren F, Mach F, Smulders Y, et al.ESC Scientific Document Group, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Eur Heart J.* 2021;42:3227–3337.

90. World Bank; Institute for Health Metrics and Evaluation. The Cost of Air Pollution: Strengthening the Economic Case for Action. Disponible en: https://openknowledge.worldbank.org/handle/10986/25013. Consultado 2 Jun 2022.
91. CE Delft. Health impacts and costs of diesel emissions in the EU – November 2018. Delft, CE Delft, November 2018. Disponible en: https://epha.org/wp-content/uploads/2018/11/embargoed-until-27-november-00-01-am-cet-time-ce-delft-4r30-health-impacts-costs-diesel-emissions-eu-def.pdf. Consultado 2 Jun 2022.