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REVIEW ARTICLE

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Pulmonary vascular disease, environmental pollution, and climate change

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Abstract

Pollution and climate change constitute a combined, grave and pervasive threat to humans and to the life-support systems on which they depend. Evidence shows a strong association between pollution and climate change on cardiovascular and respiratory diseases, and pulmonary vascular disease (PVD) is no exception. An increasing number of studies has documented the impact of environmental pollution and extreme temperatures on pulmonary circulation and the right heart, on the severity and outcomes of patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (PH), on the incidence of pulmonary embolism, and the prevalence and severity of diseases associated with PH. Furthermore, the downstream consequences of climate change impair health care systems' accessibility, which could pose unique obstacles in the case of PVD patients, who require a complex and sophisticated network of health interventions. Patients, caretakers and health care professionals should thus be included in the design of policies aimed at adaptation to and mitigation of current challenges, and prevention of further climate change. The purpose of this review is to summarize the available evidence concerning the impact of environmental pollution and climate change on the pulmonary circulation, and to propose measures at the individual, healthcare and community levels directed at protecting patients with PVD.

KEYWORDS

extreme temperatures, extreme weather events, global warming, pulmonary embolism, pulmonary hypertension

INTRODUCTION

Pollution and climate change constitute a combined, grave and pervasive threat to human health and to the life-support systems on which humans depend.[1] The ramifications include a warming of annual average temperatures, with consequent weather systems changes and a shift from stable and predictable climate to extreme temperatures and sudden, extreme weather events (e.g., hurricanes, droughts, wildfires, hot and cold spells). Pollution (i.e., the accumulation of human-produced waste in the environment) is a major cause of climate

change, as well as being responsible for 9 million preventable deaths, or 1 in 6 deaths worldwide[2]; climate change also influences air quality both directly (e.g., decreased dispersion of air pollutants during heatwaves and increased production due to wildfires[3]) and indirectly (increased emissions from power plants to counter extreme temperatures[4]). Indeed, assuming stable population and emissions, heatwaves and atmospheric stagnation are expected to increase the concentration of airborne pollutants in China by 2050, causing a 39% and 6% increase in mortality among the Chinese population, respectively.[5] The rise in global temperatures will also cause increased water pollution from oil spills,[6] and humidity and stagnant air will also increase benzene concentrations and ozone formation.[7] Food scarcity from failed crops,[8] water shortages[9] from droughts and pollution are already causing mass migrations due to inhabitable land, famine and war[10]; the disappearance of entire ecosystems is causing such severe biodiversity loss that a 6th mass extinction is frequently evoked.[11] Furthermore, the combined challenges of pollution and climate change may lead to a massive collapse of public services, and in particular of health care infrastructure.[12]

Climate change and environmental pollution have been conclusively proven to be caused predominantly by human activities, such as industrial manufacture processes, the exploitation of natural resources including intensive land use for farming, and especially by burning decayed organic matter as a fossil fuel for energy supply.[1]

Pulmonary vascular disease (PVD) is a wide range of acute and chronic disorders of the pulmonary circulation, often progressing to right heart failure and death.[13] These disorders range from highly prevalent conditions such as acute pulmonary embolism (PE)[14] and pulmonary hypertension (PH) associated with left heart and lung disease, to infrequent forms such as pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH).[15] Because of their effect on both respiratory and cardiac function, most PVDs have high morbidity and mortality; despite this, there is surprisingly little clinical attention in everyday practice as to how these diseases may be affected by pollution and climate change.

Three interconnected aspects of the environmental challenges we face today will be addressed by this review: first, the direct and indirect biological influence of pollution and climate change on endothelial cells, pulmonary circulation, pulmonary embolism and other diseases associated with PH. Second, the burden of climate change and pollution on patients with PVD, their caretakers, and health care providers. Third, solutions to adapt, mitigate and prevent the effects of pollution and climate change and improve health within the field of PVD.

DIRECT AND INDIRECT IMPACT OF CLIMATE CHANGE ON PVD

Although a thorough understanding of PH development remains elusive, several studies have shown that pollution and climate change may both have a direct impact on the pulmonary vasculature, as well as indirect effects by increasing the prevalence and severity of other diseases associated with PH (Figure 1).

Air pollution exacerbates respiratory and cardiovascular diseases and is the fourth biggest global risk factor for premature death.[16] Fine particulate matter (PM), as well as gaseous compounds such as ozone (O_2), nitrogen dioxide (NO_2), other nitrous oxides (NO_x), and sulphur dioxide (SO_2)—mostly produced by traffic and power generation, but also wildfires and industrial waste—are the main pollutants.[17] Among these, PM with a 50% cut-off aerodynamic diameter of $<2.5\,\mu m$ ($PM_{2.5}$) is of particular interest, since these very small particles can reach the alveolar space and permeate the epithelium.[25] Indoor air can be polluted by household appliances releasing, among others, methane (gas stoves[19]), biomass fumes from wood and coal[20] (cooking and heating stoves), and carbon monoxide (CO) from heaters.[21] While the link between air pollution and other cardio-respiratory diseases is well-known, the effect of air pollution on pulmonary circulation is less commonly studied (Tables 1 and 2). Water and land contamination from microplastics,[22] pesticides[23] and toxic chemical sludge from industrial waste,[24] noise pollution,[25] extreme temperatures, and the emergence of new infections favored by a changing climate are also potentially harmful to the pulmonary circulation.

Systemic and pulmonary vasculopathy, pollution and extreme temperatures

An extensive body of evidence supports the link between pollution and endothelial dysfunction, a marker of early cardiovascular disease. A recent meta-analysis[35] found that subjects with increased short-term exposure to $PM_{2.5}$ had reduced flow-mediated dilation, which is the endothelium-mediated ability to dilate systemic arteries in response to an increase in blood flow. The same study also found increased systemic arterial stiffness (measured by augmentation index or pulse wave velocity). The reduction in flow-mediated dilation was also present with long-term exposure to $PM_{2.5}$; these effects were all proportional to the dose of pollutants.[35] Indoor air pollution, noise, and exposure to heavy metals such as cadmium, lead and mercury can all interfere with the production of nitric oxide (NO) by increased oxidative

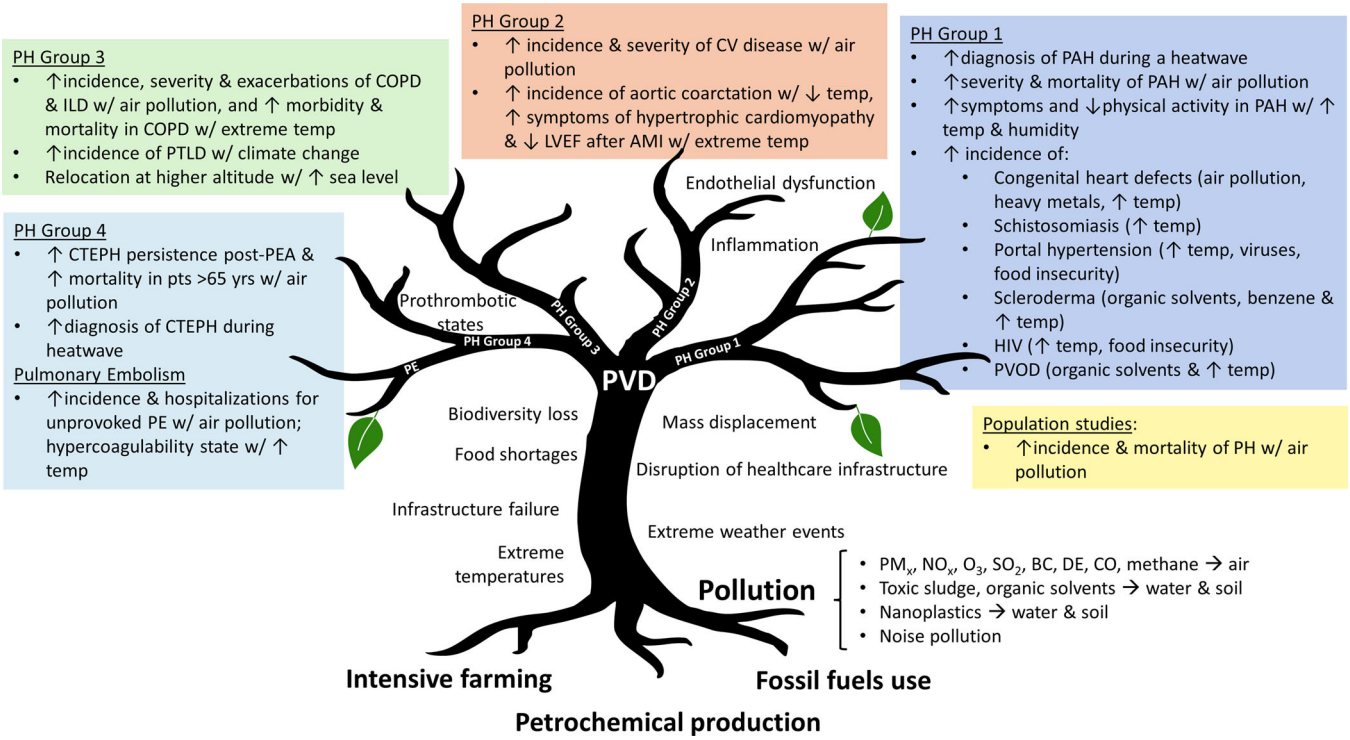

FIGURE 1 The root causes, global effects of climate change and their ramifications on PVD. Definition of abbreviations: AMI, acute myocardial infarction; BC, black carbon; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; CV, cardiovascular; DE, diesel exhaust; HIV, human immunodeficiency virus; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; NO_x, nitrogen oxides; O_3, ozone; PAH, pulmonary arterial hypertension; PE, pulmonary embolism; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PM, particulate matter; PTLD, post-tuberculosis lung disease; pts, patients; PVD, pulmonary vascular disease; PVOD, pulmonary veno-occlusive disease; SO_2, sulphur dioxide; temp, temperature; w/, with; yrs, years.

TABLE 1 Preclinical studies on pollution and climate change in pulmonary vascular disease.

Model	PH Group	Main findings
Mouse	-	Co-exposure to a weak antigen and $PM_{2.5}$ induces pulmonary arterial thickening and ↑RV in mice,[26] through IL-13, IL-17A[27] and B-cell mediated inflammation.[26]
Rabbit	-	Inhaled PM_{10} induces chronic lung inflammation and systemic endothelial dysfunction in rabbits.[28]
Mouse	1	DE induces pulmonary arterial remodelling, RV thickening and increased RV pressures in mice.[29]
Rat	1	Cold temperatures aggravate monocrotaline model of PAH through ↑expression of miR-146a-5p, miR-155-5p, TNF-α, IL-1β, and IL-6[33] and modulation of phosphodiesterase-1C.[34]
Mouse	2	Exposure to $PM_{2.5}$ aggravates RV failure by ↑lung inflammation, ↑vascular remodelling and ↑RV hypertrophy in mice with LV failure.[30,31]
Mouse	3	Co-exposure to SO_2, NO_2 and $PM_{2.5}$ triggers airflow limitation, abnormal ET-1 and eNOS expression and arteriolar remodelling through the activation of the HIF-1α pathway.[32] Early pulmonary fibrosis-like changes through DNA damage with heat exposure.[102]

Abbreviations: DE, diesel exhaust; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; Fhl-1, four and a half LIM domain protein 1; HIF-1α, hypoxia-inducible factor 1α; IL-13, interleukin-13; LV, left ventricle; NO_2, nitrogen dioxide; PM, particulate matter; SO_2, sulphur dioxide; RV, right ventricle

stress, inflammation, or both.[25] Polystyrene nanoplastics cause endothelial injury, vascular remodeling and a prothrombotic state in mice[22]; in patients who underwent carotid endarterectomy, the presence of micro- and nanoplastics in carotid plaques was associated with worse outcomes at 3 years.[73] Both extremely high and low temperatures are well-described risk factors for respiratory and cardiovascular morbidity and mortality[16,74]: hyperthermia causes dehydration, tachycardia and a hypermetabolic state, while hypothermia induces

TABLE 2 Clinical studies and reviews on the effects of air pollution and effects of climate change and pulmonary vascular disease in humans.

PVD	Subgroup	Main findings
Population studies		Endothelial dysfunction and stiffness of systemic arteries linked with exposure to air pollution.[35] Noise, air pollution and heavy metals contamination associated with ↓ NO production.[25] Cold-temperatures ↑ sPAP in Kyrgyz highlanders with and without PH.[43] ↑ incidence and mortality of PH associated with air pollutants.[36] Acute exposure to diesel exhaust ↑pulmonary vasomotor tone by ↓distensibility of pulmonary vessels at high cardiac output.[37] DE is associated with ↑ pulmonary vessels volume on CT scans.[38]
Pediatric population		Chronic exposure to air pollution associated with ↑ mPAP,[39] ↑ systemic inflammatory mediators and vasoconstrictors in children.[40]
Group 1 PH	iPAH, hPAH, dPAH	Exposure to air pollution linked to ↑ ESC/ERS risk in iPAH and hPAH, ↓ 6MWD in iPAH, hPAH, dPAH, with no effect on mortality in one study.[41] Exposure to air pollution associated with ↑mortality, ↑hemodynamic severity & ↑ESC/ERS risk in iPAH and hPAH in another study.[42] ↑incidence of PAH with heat and droughts.[80] High temperatures and humidity linked to symptom burden and ↓ physical activity.[44]
	Infectious diseases-PAH	↑ incidence of *Schistosoma* in currently unaffected areas[82]; ↑ incidence of HIV.[84]
	CHD-PAH	↑Maternal extreme heat exposure,[45] air pollution or exposure to heavy metals and organic solvents[24] ↑risk of congenital heart disease.
	Portopulmonary hypertension	↑ incidence of hepatotoxic pathogens[86]; hepatotoxicity and ↑ incidence of liver disease with ↑ temperatures.[86]
	CTD-PAH	↑ incidence of SSc[87,89] and other CTDs[87] with exposure to organic solvents, crystalline silica and welding fumes; ↓ pulmonary capillary blood flow in patients with Raynaud's phenomenon with cold temperatures.[91]
	PVOD	PVOD associated with exposure to organic solvents.[46]
Group 2 PH		Exposure to air pollution is associated with ↑ of cardiovascular disease in women[47] and ↑ LV mass.[95] Cold spells ↑ incidence of aortic coarctation[96]; extreme temperatures linked to ↑ symptoms in hypertrophic cardiomyopathy[97] and ↓ LV function after acute myocardial infarction.[98]
Group 3 PH	COPD	Air pollution is main risk factor for COPD in nonsmokers[48] and linked to ↑ incidence of COPD[50] and ↑severity of emphysema.[49] ↑mortality risk,[51,52] ↑ symptoms,[54] ↑exacerbations,[54,57,58] ↑hospitalisations[55,56] and ↓lung function[54] with extreme high and low temperatures and dust exposure.
	ILD	Association between ambient air pollution and subclinical ILD[59] and between elemental carbon and ↑risk of interstitial lung abnormalities.[60] Exposure to air pollution and incidence,[61] exacerbation,[62] and mortality[63,64] in IPF.
	PTLD	↑ incidence of tuberculosis due to climate change.[103]
	High altitude PH	Exposure to high altitude hypoxia and PH risk[106] in non-acclimatised populations due to sea level rise.[105]
	Obesity-hypoventilation	Obesity, undernutrition and climate change as a Global Syndemic.[108]
Group 4 PH	CTEPH	Exposure to air pollutants increases persistence of CTEPH post-PEA and mortality in patients >65 years old.[66] Heat and droughts increase incidence of CTEPH.[80]
Pulmonary embolism		Probable link between air pollution and venous thromboembolism[109]; air pollution associated to ↑ of hospitalization for PE of any cause.[68] Air pollution, heavy metals and organic solvents exposure associated with ↑ incidence of unprovoked PE.[67,69] Haemoconcentration, hypercoagulability and clotting factor abnormalities with extreme temperatures.[17]

TABLE 2 (Continued)

PVD	Subgroup	Main findings
Right Ventricle		Air pollution exposure associated with ↑RV mass and ↑RV end-diastolic volume.[70-72,111] Extreme temperatures may lead to tachycardia and cardiogenic shock.[17] Ineffective thermoregulation and increased vulnerability to heat in chronic heart failure patients.[112,113]

Abbreviations: 6MWD, 6-minute walking distance; CHD-PAH, congenital heart disease associated pulmonary arterial hypertension; COPD, chronic obstructive pulmonary disease; CT, computerised tomography; CTD-PAH, connective tissue disease associated pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; DE, diesel exhaust; dPAH, drug-induced pulmonary arterial hypertension; ERS, European Respiratory Society; ESC, European Society of Cardiology; HIV, human immunodeficiency virus; hPAH, heritable pulmonary arterial hypertension; ILD, interstitial lung disease; iPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis; LV, left ventricle; mPAP, mean pulmonary artery pressure; NO, nitric oxide; PE, pulmonary embolism; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVD, pulmonary vascular disease; PVOD, pulmonary veno-occlusive disease; RV, right ventricle; sPAP, systolic pulmonary artery pressure; SSc, systemic sclerosis.

vasoconstriction and increased cardiac oxygen demand.[17] All these factors may easily decompensate the fragile equilibrium of patients with PH.

In the lungs, gaseous and particulate inhaled pollution causes local inflammation.[75] Gases and smaller PM can access the bloodstream,[18] where they might directly affect NO production through increased scavenging of NO precursors by reactive oxygen species, or decreased bioavailability through reduced activity of endothelial NO synthetase.[25] Since reduced NO activity is also a key mechanism in PH, it is conceivable that pollution-caused endothelial dysfunction in the lungs may lead to vascular remodeling, and eventually to PH.

In fact, various animal models have shown that exposure to air contaminants such as PM and diesel exhaust alter the pulmonary vasculature.[26–28] Air pollution causes airway hyperresponsiveness, inflammation, pulmonary artery vasoconstriction, vascular smooth muscle cells proliferation, endothelial cell apoptosis, and pulmonary vessel remodeling in animal models.[29,32,76] Indeed, in a mouse model,[32] exposure to SO_2, NO_2, and $PM_{2.5}$ triggered airflow obstruction, inflammation, and markedly abnormal endothelin-1 (ET-1) and endothelial NO synthase expression; on histology, the pulmonary vasculature showed a significant thickening of the media and narrowing of the lumen. The pollutants also produced downregulation of miR-338-5p and increased expression of hypoxia-inducible factor-1α, which could represent a possible link between air pollution and the development of PH.[32] Mice coexposed to an inhaled antigen and $PM_{2.5}$ developed pulmonary arterial remodeling and increased right ventricular systolic pressure[76] through the action of inflammatory cytokines.[27] The role of inflammation as a mechanism of PAH is also well established,[77] and even coarser particles inhaled into the lungs, which do not transfer to the bloodstream but trigger local inflammation, may result in PH in the long term. Diesel exhaust containing NOx and aldehydes also caused a PAH phenotype in mice, with proliferation of vascular smooth muscle cells, apoptosis of endothelial cells, and an increase in right ventricular systolic pressure.[29]

Preclinical and clinical evidence shows that the pulmonary circulation may be sensitive to extreme temperatures. Indeed, cold temperatures are used to model PH and induce pulmonary arterial remodeling in rats and other animals, and its effect is modulated by phosphodiesterase-1C, which induces oxidative stress.[34] Furthermore, chronic exposure to cold temperatures aggravated a rat monocrotaline model of PAH through increased expression of miR-146a-5p, miR-155-5p, TNF-α, IL-1β, and IL-6[33]; additionally, exposure to cold (but not warm) temperatures increased echocardiography-derived systolic pulmonary artery pressure in Kyrgyz highlanders, with and without pre-existing PH.[43] Interestingly, patients with PAH have increased expression of heat-shock protein 90,[78,79] a chaperone molecule with multiple effects, including protein stabilization in response to heat and other stressors, and is also responsible for smooth muscle cell proliferation. The full extent to which extreme temperatures affect the pulmonary circulation remains to be elucidated.

Populations-based and healthy subjects studies on pulmonary vasculopathy and air pollution

A recent UK Biobank analysis of almost 500,000 participants found that the combination of air pollution and smoking had a synergistic effect on the incidence and mortality of PH, and even never-smokers had a higher risk of PH with increased exposure to $PM_{2.5}$, PM_{10}, NO_2, and NO_x.[36] In a randomized cross-over trial, 18 healthy subjects exposed for 2 h to diesel exhaust had no increase of echocardiography-measured pulmonary vascular resistance at rest, but showed an increase in pulmonary artery pressure to cardiac output slope and

decreased pulmonary distensibility during dobutamine stress test; the study found no difference in serum ET-1 and fractional exhaled NO.[37] The Multi-Ethnic Study of Atherosclerosis (MESA), involving more than 6000 subjects from six communities in the United States, evaluated total pulmonary vascular volume from chest computed tomography in 3023 patients exposed to ambient black carbon (a component of diesel exhaust), NO_2, NO_x, $PM_{2.5}$, and O_3. The study found a direct correlation between long-term exposure to black carbon and total pulmonary vasculature structures, suggesting air pollution may play a role in pulmonary vascular remodeling.[38] In Mexico City, exposure to $PM_{2.5}$ in children was associated with an increase in mean pulmonary arterial pressure, inflammatory mediators, and vasoconstrictors (including tumor necrosis factor-α, prostaglandin E-2, C-reactive protein, interleukin-1β, and ET-1).[39,40]

Finally, a study[80] of 38,746 emergency department admissions in Douglas County, Omaha, compared the odds of a diagnosis of PAH, CTEPH or right heart failure during the summer of 2012, which was marked by extremely high temperatures and drought, compared to the same months in 2011. The study found that 15 patients were diagnosed during the summer of 2012 compared to four patients in the same period in 2011, the odds ratio (OR) of a diagnosis being 4.35 (95% confidence interval [CI] 1.08−17.57) during the heatwave.

PAH (Group 1)

PAH is a rare disease of the pulmonary vasculature with distinctive pathologic features, which can be found: in the absence of other significant diseases (idiopathic PAH, iPAH); in the presence of familial history or genetic mutations (hereditary PAH, hPAH); with predominantly capillary or venular involvement (pulmonary veno-occlusive disease [PVOD] or pulmonary capillary hemangiomatosis); with exposure to certain drugs and toxins; and is associated with diseases such as connective tissue diseases (CTD), congenital heart defects, liver disease, and certain chronic infections.[15]

Despite the different associated diseases and circumstances, patients with PAH are often studied in cohort, as the underlying pathophysiology is considered to be largely similar. In a study of 15 patients with treated and stable PAH, high temperatures and humidity, especially when occurring in combination, were directly correlated with symptoms burden and inversely correlated with physical activity, compared to days with average temperature and humidity.[44]

Idiopathic, hereditary, or drug-induced PAH

Scientific evidence of the effect of air pollution in patients with idiopathic or hereditary PAH is scarce. A retrospective study,[41] conducted in Belgium with data from 211 subjects, found that patients with iPAH and hPAH had a worse European Society of Cardiology (ESC)/European Respiratory Society (ERS) abbreviated risk score when exposed to higher levels of black carbon, and that iPAH, hPAH and anorexigens-related PAH patients had lower 6-min walking distance if living near a major road; however, this study did not find an association between air pollution and mortality. By contrast, a UK National Cohort Study of iPAH and hPAH,[42] which included 301 patients, identified exposure to air pollution ($PM_{2.5}$, NO_2, and indirect traffic-related variables) as being associated with a higher risk of death or lung transplantation (adjusted HR 4.38 (95% CI 1.44–13.36) per 3 $\mu g \cdot m^{-3}$; $p = 0.009$). In the same study, residential proximity to heavy traffic was also associated with higher hemodynamic severity and ESC/ERS risk scores at baseline.

PAH associated with infectious diseases

With more than 200 million people worldwide infected with the parasite *Schistosoma*, it is estimated that around 270,000 people have schistosomiasis-associated PAH[81]; globally, this form of PAH is in fact the most common. Rising water temperatures, droughts, and increased rainfall leading to floods are expected to impact the lifecycle and spread of schistosomiasis,[82] with warmer temperatures at higher latitudes increasing the prevalence of this parasite in currently schistosomiasis-free regions.

Although PAH only affects 0.5% of HIV patients, with over 30 million infected individuals the global prevalence is estimated to be as high as 150,000 cases.[81] Furthermore, studies conducted in countries where HIV is highly prevalent, although based on echocardiography, detect a prevalence of 14%.[83] Climate change is projected to increase the incidence and prevalence of HIV due to extreme weather events, food insecurity (identified as an important factor in sexual risk-taking behavior and migration), and erosion of public health infrastructure, with subsequent disruptions of chronic treatment adherence, higher transmission rates, and drug resistance.[84]

Congenital heart disease (CHD)-associated PH

Maternal exposure to several pollutants has been associated with increased incidence of CHD. Most studies have focused on the effect of outdoor air pollution

($PM_{2.5}$, PM_{10}, SO_2, and NO_2), indoor solid fossil fuel (coal and wood) burning in stoves and heating systems, heavy metal exposure[85] (arsenic, nickel, cadmium, manganese, or lead) from industry waste, organochlorine pesticides, and organic solvents.[24]

Extreme heat exposure during pregnancy is also associated with increased incidence of CHD.[45] Interestingly, some of these exposures might have synergistic effects,[85] while others may be disease-specific and vary according to the amount of exposure. CHD is associated with PAH in 3-7% of the adult population and depends on several factors, including type of CHD and age of surgical correction.[15]

Portopulmonary hypertension

The increased environmental occurrence of schistosomiasis has already been discussed; this and other parasitic infections are hepatotoxic, as are the viruses causing Hepatitis A and E, fungal aflatoxins, and cyanobacteria, all of which are likely to thrive with the rise in global temperatures.[86] Hyperthermia is also cytotoxic to hepatocytes and can cause reduced hepatic blood flow. Furthermore, climate change-related food insecurity, mental health burdens, and air pollution can all directly or indirectly cause liver disease, as highlighted in a commentary from four major liver disease scientific societies.[86] PAH occurs in 2–6% of patients with portal hypertension[15] and significantly increases their morbidity and mortality.

Connective tissue disease-associated PH

Organic solvents are compounds commonly used in manufacturing, and feature predominantly in cleaning products, varnish, paint, and degreasing agents. They are an occupational exposure for workers of the many industries that use them, but they also affect the general population by polluting air, water and soil as industrial toxic waste. Other organic solvents such as benzene are even more common, and are fundamental components of a wide range of products, including plastics (polystyrene), dyes, resins and adhesives, nylon, detergents and pesticides, and gasoline; therefore, they are highly pervasive substances.

The incidence of CTD has been associated with chemical exposures—particularly that of organic solvents such as trichlorethylene, acetone and aromatic hydrocarbons—since the 1970s. A systematic review and meta-analysis[87] found that exposure to organic solvents was significantly associated with an increased risk of developing autoimmune diseases, among which systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) are the CTDs most commonly associated with PAH. A previous meta-analysis, focusing specifically on SSc, found an increased risk (relative risk 2.91, 95% CI 1.60 ± 6.00) of developing SSc with exposure to different types of organic solvents.[88] In addition to organic solvents, in a prospective study,[89] the risk of developing SSc was related to increased exposure to crystalline silica and welding fumes. Precapillary PH is associated with SSc in 5–19% of cases[15] and with SLE in 5% of cases,[90] and its presence conditions a high burden of symptoms and complications; in SSc-PAH patients, overall survival is particularly poor.[15] Patients with Raynaud's phenomenon, a common manifestation of CTD, also show reduced pulmonary capillary blood flow when exposed to cold temperatures.[91] Moreover, benzene air pollution is increased by humidity and decreased by wind, meaning the humid and stagnant air typical of warmer climates would likely intensify its concentration; meanwhile, the global elevation in temperatures is projected to increase its ability to pollute water supplies in the event of an oil spill in proximity with groundwater.[6] Similarly, pollution from persistent organic pollutants, such as those contained in pesticides, is expected to increase due to climate change.[92,93]

PVOD

PVOD is a highly aggressive form of precapillary PH for which there is no established medical therapy, and the only effective treatment is lung transplant in eligible patients.[15] As with CTD, PVOD also presents increased incidence following exposure to organic solvents,[46] particularly trichlorethylene. Interestingly, some cases of SSc-PAH present features of PVOD,[94] which may be at least partly the result of a common etiopathogenesis. In a case-control study,[46] the OR, adjusted for age, sex, and smoking history of developing PVOD when exposed to organic solvents as a whole, was 12.8 (95% CI 2.7–60.8), while in the specific case of trichlorethylene the adjusted OR was 8.2 (95% CI 1.4–49.4). Other significant exposures included paint, varnish, glue, degreasing agents, kerosene, welding fumes and silica.[46] As previously mentioned, the rise in global temperatures is projected to directly and indirectly increase exposure to organic solvents.[92,93]

PH associated with heart diseases (Group 2)

Despite abundant evidence on the association between cardiovascular disease, pollution and climate change,

there are no clinical studies focusing specifically on their effect on PH associated with left heart disease (LHD). However, some preclinical and clinical clues show a potential link between pollution, extreme temperatures, and LHD-associated PH.

Air pollution not only increases the incidence of LHD,[47] but preliminary animal studies have found a worsening of PH in a left ventricle failure mouse model (through transverse aortic constriction) when exposed to $PM_{2.5}$,[30,31] and a MESA study found greater left ventricular mass in subjects exposed to higher air pollution.[95] Furthermore, cold spells during pregnancy have been linked to increased incidence of congenital artic coarctation,[96] while temperature extremes may be associated with increased symptoms of hypertrophic cardiomyopathy[97] and with lower left ventricular ejection fraction after myocardial infarction.[98] All of these conditions are recognized causes[99,100] of Group 2 PH.

PH associated with lung diseases or hypoxia (Group 3)

The direct influence of pollution and climate change on PH associated with lung disease has not yet been studied, but its effect on the prevalence and severity of parenchymal diseases has been extensively described.

The role of air pollution in the development, exacerbation and progression of parenchymal lung diseases is well–known for chronic obstructive pulmonary disease (COPD) and lung fibrosis.[48,101] In non-smoking subjects, air pollution is the main risk factor for developing COPD.[48] Exposure to O_3, $PM_{2.5}$, NO_x, and black carbon is associated with the severity of emphysema[49] and higher exposure to $PM_{2.5}$, PM_{10}, and NO_2 leads to increased incidence of COPD.[50] A recent report from the Global Initiative for Chronic Obstructive Lung Disease emphasizes that there is no safe threshold of air pollution, and that as many as 8% of COPD deaths can be attributed to climate change.[48] Indeed, in COPD patients, mortality risk was found[51] to be higher (HR 1.037, 95% CI 1.019−1.055) for each 1°C increase in yearly summer temperatures across 135 US cities, adjusted for O_3 levels, with a similar risk in chronic heart failure patients (HR 1.028, 95% CI 1.013-1.042); interestingly, among the more than 3 million patients with COPD, 27% had chronic heart failure, while 21% of the almost 2 million patients with chronic heart failure also suffered from COPD. Cold temperatures are also associated with mortality in COPD patients,[52] and both hot and cold temperature extremes,[53] and even desert dust exposure[57] associated with increasing global warming and desertification, may be related to worse symptoms, decreased lung function,[54] exacerbations,[58] and hospitalizations[55,56] in COPD.

Interstitial lung disease (ILD) is also affected by poor air quality. The Framingham heart study found an increased risk for development of interstitial lung abnormalities associated with traffic-related pollution,[60] and a MESA study correlated it with subclinical ILD.[59] Several other studies have found a direct relationship between exposure to NO_2 and idiopathic pulmonary fibrosis incidence[61] and exacerbations,[62] as well as between exposure to $PM_{2.5}$, PM_{10}, and CO and idiopathic pulmonary fibrosis mortality.[63,64] The link between extreme temperatures and weather events and ILD is less established, although preclinical evidence suggests that heat exposure might induce early fibrosis-like changes through DNA damage.[102]

Even post-tuberculosis lung disease, a thus-far neglected cause of PH, may become more common due to the relationship between climate change and known risk factors (HIV infection, diabetes mellitus, undernutrition, overcrowding, poverty, and indoor air pollution).[103] The prevalence of PH in post-tuberculosis lung disease is estimated at 48%.[104]

More than 200 million people live in places that sea level rise will affect by 2100.[105] Relocation to higher altitudes may expose unacclimatised populations to hypoxia, increasing the risk of high altitude PH.[106]

Finally, obesity, sleep apnoea, and nocturnal hypoventilation may cause PH[107] in up to 42% of patients with very high body mass index.[15] Although PH is usually mild-moderate in these patients, the association of obesity, undernutrition and climate change have been labeled a Global Syndemic.[108]

Pulmonary embolism and CTEPH (Group 4)

A systemic literature review[109] including more than 500,000 thromboembolic events (albeit limited by the heterogeneity of the studies included), concluded that a link between PM and venous thromboembolism is likely. In previous studies, the incidence of hospitalizations for PE of any cause was increased with exposure to $PM_{2.5}$, PM_{10}, CO, O_3, NO_2, and SO_2[68]; the incidence of unprovoked PE was also associated with exposure to PM_{10}, NO_x, SO_2, O_3, nickel, lead, arsenic, benzene, and benzopyrene.[67,69] Moreover, extreme hot and cold ambient temperatures can both induce haemoconcentration, hypercoagulability and clotting factor abnormalities,[17] which may be mechanistic explanations for the increased incidence of both unprovoked and provoked PE.

In patients with CTEPH, exposure to $PM_{2.5}$, PM_{10}, and NO_2 has been associated with persistent PH after

pulmonary endarterectomy, and PM increase was linked to all-cause mortality in patients > 65 years[66]; in a large European registry,[65] the average age for CTEPH patients was found to be 63 years old. Furthermore, exposure to inhaled pollutants has been associated with inflammation,[66] an important pathogenetic mechanism of CTEPH.[110] Finally, as previously mentioned, one study[80] found an increased incidence in the diagnosis of CTEPH during a season of extreme heat and drought.

Right ventricle

Multiple studies have shown that exposure to inhaled pollutants may alter the heart structure and function. The MESA study has found that subjects exposed to NO_2,[70] $PM_{2.5}$[71] and $PM_{2.5–10}$ [72] have greater right ventricular mass and right ventricular end-diastolic volume. Similar results were found in the UK Biobank Population Imaging Study.[111] The effects of extreme hot and cold spells, including increased body temperature leading to dehydration and sympathetic activation, can induce tachycardia and cardiogenic shock; moreover, extreme heat can induce hypermetabolism, leading to increased oxygen demand.[17] Interestingly, some of the physiological coping mechanisms to extreme temperatures might be impaired in patients with chronic heart failure, explaining the ineffective thermoregulation and increased vulnerability to heat observed in these patients.[112,113]

EFFECTS OF CLIMATE CHANGE ON PVD PATIENT CARE

Besides the direct impact that pollution and climate change have on the pulmonary circulation and the increase in prevalence and severity of associated diseases, their effects on society and infrastructure might hinder the health care system's ability to deliver adequate support for patients with PE or PH.

Wildfires, hurricanes and floods have been shown to prevent access to health care,[114] all the while aggravating chronic respiratory disease.[115–117] For example, patients and health care workers affected by wildfires[118,119] and hurricanes reported disrupted access to doctor consultations, medication,[120] or life-saving treatments[114]; in some studies, this was associated with increased mortality.[121] Although these challenges are not specific to PVD—the disruption to health care access due to extreme weather events, extreme temperatures and migrations affects everyone—PH patients require a complex network of care,[15] which could prove harder to provide as the effects of climate change increase. An onsite PE response team, for instance, may provide improved survival and reduced complications.[14,122] The 2022 ESC/ERS PH guidelines[15] recommend that PH centers include personnel from different medical specialties, highly trained nurses, physiotherapists, and psychologists; social workers might also be needed in cases requiring adapted housing, complex surgery (e.g., pulmonary endarterectomy), or relocation near a lung transplant program. The guidelines also suggest that PH centers should work in coordination across the health care territory, with supra-national organizations such as the European Reference Network on rare respiratory diseases or scientific societies harmonizing standards of care.

These coordinated efforts, as well as community health care services (ambulances, oxygen delivery, at-home ancillary care) or drug production and supply can all be suddenly interrupted by extreme weather events that affect telecommunications, power grids, and transport infrastructures. The emergence of new infectious diseases, favored by climate change,[123] may require shielding at home and further complicate patient care; e-health solutions may become useless when telecommunication systems fail because of floods,[124] hurricanes, or wildfires. Extreme temperatures may make traveling to the hospital impossible for fragile patients.[125] In cases of extreme heat, patients with PH who are treated with parenteral prostanoids should also be aware of the faster flow rate of their medication during extreme heat.[126]

Preventive, mitigating and adaptive measures

A change in life habits (e.g., active transportation and lifestyle,[127,128] a plant-based diet,[129,130] smoke cessation), besides helping to reduce carbon emissions, is a useful preventive measure to reduce the incidence of heart and lung diseases commonly associated with PH, although there is no study on how this may affect PVD itself.[131,132] Individual actions, however, are not sufficient to address the double global challenge of climate change and pollution, which has both systemic root causes and systemic effects.[17] Intersectionality, i.e. the compounded impact of low socioeconomic status, difficult access to health care, and a disproportionate vulnerability to the climate crisis [1,133] may result in the paradox of policies designed to reduce air pollution mostly benefiting subjects with higher socioeconomic status.[134] Patients, caretakers and health care professionals should be involved in the design of policies to reduce emissions (focusing on shifting from fossil fuels to renewable energy) and curb pollution, as their perspective is essential to the development of adaptive, mitigating and preventive strategies (Figure 2).

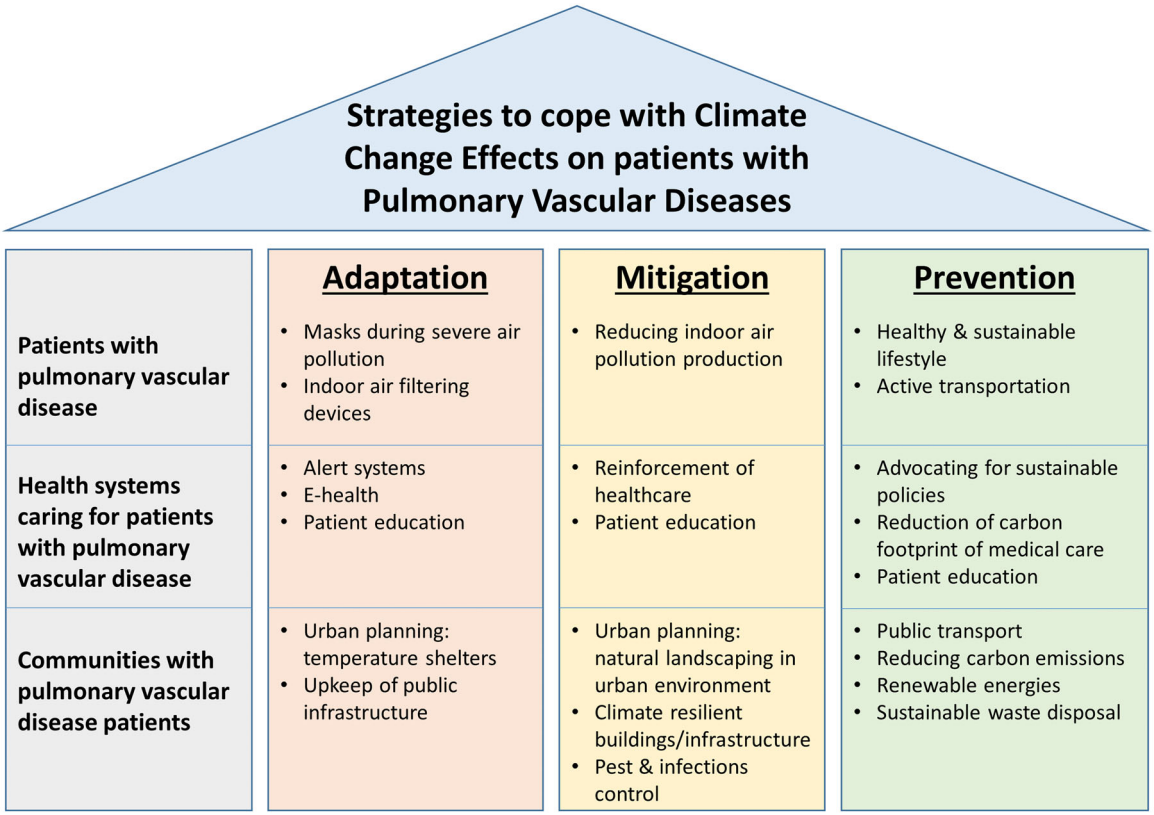

FIGURE 2 Coping strategies for climate change effects on patients with pulmonary vascular disease.

Some proposed adaptive measures include creating alert systems for vulnerable individuals and increasing the capacity of health care facilities during extreme temperatures or weather events.[17] At the individual level, some studies suggest there are benefits to wearing N95 masks during wildfires[135] or using air filtering systems for air pollution[136]; respiratory disease patients may also be advised to avoid heating their homes by burning wood or biomass, and to improve indoor ventilation.[48] Longer term policies at the community level involve the use of nature landscaping in urban areas to reduce heat and build temperature shelters, and climate-resilient buildings.[17] Preventive measures include greatly improving public and active transportation options, regulating waste disposal (especially at the industrial level), and reducing new building plans. Further research is needed to verify the beneficial effects of these strategies in the different geographical and community contexts, as well as its relevance to patients with PVD.

Finally, the health sector has a huge impact on emissions through industrial production, waste and energy consumption,[137,138] and the multi-dimensional evaluation of PH recommended in the current guidelines' diagnostic algorithm requires energy-intensive, waste-producing procedures.[15] A simpler diagnostic process would not only reduce health care-related costs and waste, but also expose patients to less complications. Further research may find simpler, more efficient diagnostic tools and better risk assessment scores to reduce health care overuse in stable, low-risk patients who could benefit from e-health solutions[139,140]; in parallel, close monitoring and early treatment in high-risk patients may arguably reduce hospitalizations. After efficacy and safety, which are the highest priorities in patient-centered health care, health care managers may wish to consider the environmental efficiency of medical interventions: low environmental-impact solutions such as physical therapy[141] are safe and effective[142] in stable PAH and CTEPH patients, and home rehabilitation[143] may further reduce the need for transportation.

FUTURE DIRECTIONS OF RESEARCH ON CLIMATE CHANGE, POLLUTION AND PVD

The global challenge of climate change and environmental pollution to PVD requires further study on several aspects, from its biological links to the organization of health care resources. We suggest the following areas of particular interest:

- Original research on molecular pathways and lung vascular pathology, as well as pathophysiological studies on the right and left heart, designed to untangle the effects of exposure to pollutants and extreme temperatures on PVD patients.
- Epidemiologic studies to uncover the link between pollution, extreme temperatures and weather events and the prevalence and phenotype of PVD, ideally taking into account the intersectional effects of socioeconomic and geographic factors.
- Research into the role of lifestyle measures such as active transportation, a plant-based diet and smoke cessation on the outcomes of PVD patients.
- Surveys and population-based studies elucidating the burden of extreme weather events and extreme temperatures on healthcare access, drug supply and healthcare community service availability for PVD patients, as well as the factors that most influence this burden. Ideally, these could inform specifically designed policies to adapt, mitigate and prevent potential disruptions caused by climate change to PVD patients' life and care; the efficacy of these policies should be assessed prospectively.
- Investigations into the feasibility, efficacy and outcomes of a simplified diagnostic algorithm for PH patients as well as a diversified approach to monitoring according to disease stability and severity, which might favor increased quality of life, reduced need for hospitalization and complications in PVD patients while reducing the carbon footprint of clinical practice.

CONCLUSIONS

Climate change and environmental pollution are severe threats to human health. They both affect the pulmonary circulation, the prevalence and severity of diseases associated with PH, and the accessibility and efficiency of health care interventions, which are particularly complex for PVD patients. Mitigation, adaptation and prevention strategies, especially at the community level, are fundamental to preserve the health of PE and PH patients. Health care providers, together with patients and carers, should thus be at the forefront of the policy-making process.

AUTHOR CONTRIBUTIONS

Mona Lichtblau and **Lucilla Piccari**: Conception, design, literature research, and draft of manuscript. **Lena Reimann**: Literature research, manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

L. P. reports research grants from Janssen and Ferrer; personal fees from Janssen, Ferrer, United Therapeutics, M. S. D. and Liquidia, not related to this article. M. L. reports travel grants and honoraria from M. S. D., Janssen and Orpha Swiss, not related to this article. L. M. declares no conflict of interest.

DATA AVAILABILITY STATEMENT

No data has been generated in relation to this manuscript.

ETHICS STATEMENT

Not applicable.

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REFERENCES

1. IPCC. Climate Change 2023: Synthesis Report. Contribution of Working Groups I, II and III to the Sixth Assessment Report of the Intergovernmental Panel on Climate Change. Geneva, Switzerland: IPCC; 2023.
2. Fuller R, Landrigan PJ, Balakrishnan K, Bathan G., Bose-O'Reilly S, Brauer M, Caravanos J, Chiles T, Cohen A, Corra L, Cropper M, Ferraro G, Hanna J, Hanrahan D, Hu H, Hunter D, Janata G, Kupka R, Lanphear B, Lichtveld M, Martin K, Mustapha A, Sanchez-Triana E, Sandilya K, Schaefli L, Shaw J, Seddon J, Suk W, Téllez-Rojo MM, Yan C. Pollution and health: a progress update. Lancet Planet Health. 2022;6:e535–47. https://doi.org/10.1016/S2542-5196(22)00090-0
3. Zhang D, Wang W, Xi Y, Bi J, Hang Y, Zhu Q, Pu Q, Chang H, Liu Y. Wildland fires worsened population exposure to PM(2.5) pollution in the contiguous United States. Environm Sci Technol. 2023;57:19990–8. https://doi.org/10.1021/acs.est.3c05143
4. Kinney PL. Climate change, air quality, and human health. Am J Prev Med. 2008;35:459–67. https://doi.org/10.1016/j.amepre.2008.08.025
5. Hong C, Zhang Q, Zhang Y, Davis SJ, Tong D, Zheng Y, Liu Z, Guan D, He K, Schellnhuber HJ. Impacts of climate change on future air quality and human health in China. Proc Nat Acad Sci. 2019;116:17193–200. https://doi.org/10.1073/pnas.1812881116
6. Almaliki AJD, Bashir MJK, Llamas Borrajo JF. The impact of climate change and soil classification on benzene concentration in groundwater due to surface spills of hydraulic fracturing fluids. Water. 2022;14:1202. https://doi.org/10.3390/w14081202

7. Kumari P, Soni D, Aggarwal SG, Singh K. Seasonal and diurnal measurement of ambient benzene at a high traffic inflation site in Delhi: health risk assessment and its possible role in ozone formation pathways. Environ Analy Health Toxicol. 2023;38:e2023016–2023010. https://doi.org/10.5620/eaht.2023016
8. Kornhuber K, Lesk C, Schleussner CF, Jägermeyr J, Pfleiderer P, Horton RM. Risks of synchronized low yields are underestimated in climate and crop model projections. Nat Commun. 2023;14(3528):3528. https://doi.org/10.1038/s41467-023-38906-7
9. Davis KF, Rulli MC, Garrassino F, Chiarelli D, Seveso A, D'Odorico P. Water limits to closing yield gaps. Advan Water Reso. 2017;99:67–75. https://doi.org/10.1016/j.advwatres.2016.11.015
10. Mehrabi Z. Food system collapse. Nat Clim Chan. 2020;10:16–7. https://doi.org/10.1038/s41558-019-0643-1
11. The Lancet Planetary H. A sixth mass extinction? why planetary health matters. Lancet Planet Health. 2017;1:e163. https://doi.org/10.1016/S2542-5196(17)30083-9
12. Butkus R, Rapp K, Cooney TG, Engel LS. Envisioning a better U.S. health care system for all: reducing barriers to care and addressing social determinants of health. Ann Int Med. 2020;172:S50–9. https://doi.org/10.7326/M19-2410
13. Brittain EL, Hemnes AR. Introduction to review series on pulmonary vascular disease and right ventricular heart failure. Circ Res. 2022;130:1362–4. https://doi.org/10.1161/CIRCRESAHA.122.321168
14. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Áinle FN, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL, The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the european respiratory society (ERS): the task force for the diagnosis and management of acute pulmonary embolism of the european society of cardiology (ESC). Eur Respir J. 2019;54:1902647. https://doi.org/10.1183/13993003.01647-2019
15. Humbert M, Kovacs G, Hoeper MM. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2022;61(1):2200879. https://doi.org/10.1183/13993003.00879-2022
16. Murray CJL., Aravkin AY, Zheng P, Abbafati C, Abbas KM, Abbasi-Kangevari M, Abd-Allah F, Abdelalim A, Abdollahi M, Abdollahpour I, Abegaz KH, Abolhassani H, Aboyans V, Abreu LG, Abrigo MRM, Abualhasan A, Abu-Raddad LJ, Abushouk AI, Adabi M, Adekanmbi V, Adeoye AM, Adetokunboh OO, Adham D, Advani SM, Agarwal G, Aghamir SMK, Agrawal A, Ahmad T, Ahmadi K, Ahmadi M, Ahmadieh H, Ahmed MB, Akalu TY, Akinyemi RO, Akinyemiju T, Akombi B, Akunna CJ, Alahdab F, Al-Aly Z, Alam K, Alam S, Alam T, Alanezi FM, Alanzi TM, Alemu B, Alhabib KF, Ali M, Ali S, Alicandro G, Alinia C, Alipour V, Alizade H, Aljunid SM, Alla F, Allebeck P, Almasi-Hashiani A, Al-Mekhlafi HM, Alonso J, Altirkawi KA, Amini-Rarani M, Amiri F, Amugsi DA, Ancuceanu R, Anderlini D, Anderson JA, Andrei CL, Andrei T, Angus C, Anjomshoa M, Ansari F, Ansari-Moghaddam A, Antonazzo IC, Antonio CAT, Antony CM, Antriyandarti E, Anvari D, Anwer R, Appiah SCY, Arabloo J, Arab-Zozani M, Ariani F, Armoon B, Ärnlöv J, Arzani A, Asadi-Aliabadi M, Asadi-Pooya AA, Ashbaugh C, Assmus M, Atafar Z, Atnafu DD, Atout MMW, Ausloos F, Ausloos M, Ayala Quintanilla BP, Ayano G, Ayanore MA, Azari S, Azarian G, Azene ZN, Badawi A, Badiye AD, Bahrami MA, Bakhshaei MH, Bakhtiari A, Bakkannavar SM, Baldasseroni A, Ball K, Ballew SH, Balzi D, Banach M, Banerjee SK, Bante AB, Baraki AG, Barker-Collo SL, Bärnighausen TW, Barrero LH, Barthelemy CM, Barua L, Basu S, Baune BT, Bayati M, Becker JS, Bedi N, Beghi E, Béjot Y, Bell ML, Bennitt FB, Bensenor IM, Berhe K, Berman AE, Bhagavathula AS, Bhageerathy R, Bhala N, Bhandari D, Bhattacharyya K, Bhutta ZA, Bijani A, Bikbov B, Bin Sayeed MS, Biondi A, Birihane BM, Bisignano C, Biswas RK, Bitew H, Bohlouli S, Bohluli M, Boon-Dooley AS, Borges G, Borzì AM, Borzouei S. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. Lancet. 2020;396:1223–49. https://doi.org/10.1016/S0140-6736(20)30752-2
17. Khraishah H, Alahmad B, Ostergard Jr. RL, AlAshqar A, Albaghdadi M, Vellanki N, Chowdhury MM, Al-Kindi SG, Zanobetti A, Gasparrini A, Rajagopalan S. Climate change and cardiovascular disease: implications for global health. Nat Revi Cardiol. 2022;19:798–812. https://doi.org/10.1038/s41569-022-00720-x
18. Miller MR, Raftis JB, Langrish JP, McLean SG, Samutrtai P, Connell SP, Wilson S, Vesey AT, Fokkens PHB, Boere AJF, Krystek P, Campbell CJ, Hadoke PWF, Donaldson K, Cassee FR, Newby DE, Duffin R, Mills NL. Inhaled nanoparticles accumulate at sites of vascular disease. ACS Nano. 2017;11:4542–52. https://doi.org/10.1021/acsnano.6b08551
19. Lebel ED, Michanowicz DR, Bilsback KR, Hill LAL, Goldman JSW, Domen JK, Jaeger JM, Ruiz A, Shonkoff SBC. Composition, emissions, and air quality impacts of hazardous air pollutants in unburned natural gas from residential stoves in california. Environ Sci Technol. 2022;56:15828–38. https://doi.org/10.1021/acs.est.2c02581
20. Torres-Duque C, Maldonado D, Perez-Padilla R, Ezzati M, Viegi G. Biomass fuels and respiratory diseases: a review of the evidence. Proc American Thor Soc. 2008;5:577–90. https://doi.org/10.1513/pats.200707-100RP
21. Bentayeb M, Norback D, Bednarek M, Bernard A, Cai G, Cerrai S, Eleftheriou KK, Gratziou C, Holst GJ, Lavaud F, Nasilowski J, Sestini P, Sarno G, Sigsgaard T, Wieslander G, Zielinski J, Viegi G, Annesi-Maesano I. Indoor air quality, ventilation and respiratory health in elderly residents living in nursing homes in Europe. Eur Respir J. 2015;45:1228–38. https://doi.org/10.1183/09031936.00082414
22. Wang X, Jia Z, Zhou X, Su L, Wang M, Wang T, Zhang H. Nanoplastic-induced vascular endothelial injury and

coagulation dysfunction in mice. Scie Total Environ. 2023;865:161271. https://doi.org/10.1016/j.scitotenv.2022.161271
23. Ghosh R, Siddharth M, Singh N, Kare PK, Banerjee BD, Wadhwa N, Tripathi AK. Organochlorine Pesticide-Mediated induction of NADPH oxidase and Nitric-Oxide synthase in endothelial cell. J Clin Diagn Res. 2017;11:09. https://doi.org/10.7860/JCDR/2017/25276.9315
24. Gorini F, Chiappa E, Gargani L, Picano E. Potential effects of environmental chemical contamination in congenital heart disease. Ped Cardiol. 2014;35:559–68. https://doi.org/10.1007/s00246-014-0870-1
25. Bayo Jimenez MT, Hahad O, Kuntic M. Noise, air, and heavy metal pollution as risk factors for endothelial dysfunction. Eur Cardiol. 2023;18:e09. https://doi.org/10.15420/ecr.2022.41
26. Park SH, Chen WC, Durmus N, Bleck B, Reibman J, Riemekasten G, Grunig G. The effects of Antigen-Specific IgG1 antibody for the Pulmonary-Hypertension-Phenotype and B cells for inflammation in mice exposed to antigen and fine particles from air pollution. PLoS One. 2015;10:e0129910. https://doi.org/10.1371/journal.pone.0129910
27. Park SH, Chen WC, Esmaeil N, Lucas B, Marsh LM, Reibman J, Grunig G. Interleukin 13- and interleukin 17A-induced pulmonary hypertension phenotype due to inhalation of antigen and fine particles from air pollution. Pulm Circ. 2014;4:654–68. https://doi.org/10.1086/678511
28. Tamagawa E, Bai N, Morimoto K, Gray C, Mui T, Yatera K, Zhang X, Xing L, Li Y, Laher I, Sin DD, Man SFP, van Eeden SF. Particulate matter exposure induces persistent lung inflammation and endothelial dysfunction. American J Physiol Lung Cellu Mol Physiol. 2008;295:L79–85. https://doi.org/10.1152/ajplung.00048.2007
29. Liu J, Ye X, Ji D, Zhou X., Qiu C, Liu W, Yu L. Diesel exhaust inhalation exposure induces pulmonary arterial hypertension in mice. Environm Poll. 2018;237:747–55. https://doi.org/10.1016/j.envpol.2017.10.121
30. Chen JJ, Ma WM, Yuan JL, Cui LQ. PM2.5 exposure aggravates left heart failure induced pulmonary hypertension. Acta Cardiologica. 2019;74:238–44. https://doi.org/10.1080/00015385.2018.1488568
31. Yue W, Tong L, Liu X, Weng X, Chen X, Wang D, Dudley SC, Weir EK, Ding W, Lu Z, Xu Y, Chen Y. Short term Pm2.5 exposure caused a robust lung inflammation, vascular remodeling, and exacerbated transition from left ventricular failure to right ventricular hypertrophy. Redox Biol. 2019;22:101161. https://doi.org/10.1016/j.redox.2019.101161
32. Ji X, Zhang Y, Ku T, Yun Y., Li G, Sang NMicroRNA-338-5p modulates pulmonary hypertension-like injuries caused by SO2, NO2and PM2.5co-exposure through targeting the HIF-1α/Fhl-1 pathway. Toxicol Res. 2016;5:1548–60. https://doi.org/10.1039/c6tx00257a
33. Sanchez-Gloria JL, Carbo R, Buelna-Chontal M. Cold exposure aggravates pulmonary arterial hypertension through increased miR-146a-5p, miR-155-5p and cytokines TNF-alpha, IL-1beta, and IL-6. Life Sci. 2021;287:120091. https://doi.org/10.1016/j.lfs.2021.120091
34. Crosswhite P, Sun Z. Inhibition of phosphodiesterase-1 attenuates cold-induced pulmonary hypertension. Hypertension. 2013;61:585–92. https://doi.org/10.1161/HYPERTENSIONAHA.111.00676
35. Li J, Liu F, Liang F, Yang Y., Lu X., Gu D. Air pollution exposure and vascular endothelial function: a systematic review and meta-analysis. Environ Sci Pollut Res, 2023, 30:28525–49. https://doi.org/10.1007/s11356-023-25156-9
36. Shi H, Chen L, Zhang S, Li R., Wu Y., Zou H., Wang C., Cai M., Lin H. Dynamic association of ambient air pollution with incidence and mortality of pulmonary hypertension: A multistate trajectory analysis. Ecotoxicol Environm Saf. 2023;262:115126. https://doi.org/10.1016/j.ecoenv.2023.115126
37. Wauters A, Vicenzi M, De Becker B, Riga JP, Esmaeilzadeh F, Faoro V, Vachiéry JL, van de Borne P, Argacha JF. At high cardiac output, diesel exhaust exposure increases pulmonary vascular resistance and decreases distensibility of pulmonary resistive vessels. American J Physiol Heart Circ Physiol. 2015;309:H2137–44. https://doi.org/10.1152/ajpheart.00149.2015
38. Aaron CP, Hoffman EA, Kawut SM, Austin JHM, Budoff M, Michos ED, Hinckley Stukovsky K, Sack C, Szpiro AA, Watson KD, Kaufman JD, Barr RG. Ambient air pollution and pulmonary vascular volume on computed tomography: the MESA air pollution and lung cohort studies. Eur Respir J. 2019;53:1802116. https://doi.org/10.1183/13993003.02116-2018
39. Calderón-Garcidueñas L, Vincent R, Mora-Tiscareño A, Franco-Lira M, Henríquez-Roldán C, Barragán-Mejía G, Garrido-García L, Camacho-Reyes L, Valencia-Salazar G, Paredes R, Romero L, Osnaya H, Villarreal-Calderón R, Torres-Jardón R, Hazucha MJ, Reed W. Elevated plasma endothelin-1 and pulmonary arterial pressure in children exposed to air pollution. Environ Health Perspect. 2007;115:1248–53. https://doi.org/10.1289/ehp.9641
40. Calderón-Garcidueñas L, Villarreal-Calderon R, Valencia-Salazar G, Henríquez-Roldán C, Gutiérrez-Castrellón P, Torres-Jardón R, Osnaya-Brizuela N, Romero L, Torres-Jardón R, Solt A, Reed W. Systemic inflammation, endothelial dysfunction, and activation in clinically healthy children exposed to air pollutants. Inhalat Toxicol. 2008;20:499–506. https://doi.org/10.1080/08958370701864797
41. Swinnen K, Bijnens E, Casas L, Nawrot TS, Delcroix M, Quarck R, Belge C. Health effects of exposure to residential air pollution in patients with pulmonary arterial hypertension: a cohort study in Belgium. Eur Respir J. 2022;60:2102335. https://doi.org/10.1183/13993003.02335-2021
42. Sofianopoulou E, Kaptoge S, Gräf S, Hadinnapola C, Treacy CM, Church C, Coghlan G, Gibbs JSR, Haimel M, Howard LS, Johnson M, Kiely DG, Lawrie A, Lordan J, MacKenzie Ross RV, Martin JM, Moledina S, Newnham M, Peacock AJ, Price LC, Rhodes CJ, Suntharalingam J, Swietlik EM, Toshner MR, Wharton J, Wilkins MR, Wort SJ, Pepke-Zaba J, Condliffe R, Corris PA, Di Angelantonio E, Provencher S, Morrell NW. Traffic exposures, air pollution and outcomes in pulmonary arterial hypertension: a UK cohort study analysis. Eur Respir J. 2019;53:1801429. https://doi.org/10.1183/13993003.01429-2018

43. Sydykov A, Maripov A, Muratali Uulu K, Kushubakova N, Petrovic A, Vroom C, Cholponbaeva M, Duishobaev M, Satybaldyev S, Satieva N, Mamazhakypov A, Sartmyrzaeva M, Omurzakova N, Kerimbekova Z, Baktybek N, Pak O, Zhao L, Weissmann N, Sarybaev A, Avdeev S, Ghofrani HA, Schermuly RT, Kosanovic D. Pulmonary vascular pressure response to acute cold exposure in Kyrgyz highlanders. High Altit Med Biol. 2019;20:375–82. https://doi.org/10.1089/ham.2019.0046
44. Jehn M, Gebhardt A, Liebers U, Kiran B, Scherer D, Endlicher W, Witt C. Heat stress is associated with reduced health status in pulmonary arterial hypertension: a prospective study cohort. Lung. 2014;192:619–24. https://doi.org/10.1007/s00408-014-9587-4
45. Zhang W, Spero TL, Nolte CG, Garcia VC, Lin Z, Romitti PA, Shaw GM, Sheridan SC, Feldkamp ML, Woomert A, Hwang SA, Fisher SC, Browne ML, Hao Y, Lin S, Hobbs C, Carmichael S, Reefhuis J, Tinker S, Anderka M, Druschel C, Bell E, Olshan A, Meyer R, Canfield M, Langlois P, Botto L. Projected changes in maternal heat exposure during early pregnancy and the associated congenital heart defect burden in the United States. J Am Heart Assoc. 2019;8:e010995. https://doi.org/10.1161/JAHA.118.010995
46. Montani D, Lau EM, Descatha A, Jaïs X, Savale L, Andujar P, Bensefa-Colas L, Girerd B, Zendah I, Le Pavec J, Seferian A, Perros F, Dorfmüller P, Fadel E, Soubrier F, Sitbon O, Simonneau G, Humbert M. Occupational exposure to organic solvents: a risk factor for pulmonary veno-occlusive disease. Eur Respir J. 2015;46:1721–31. https://doi.org/10.1183/13993003.00814-2015
47. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, Kaufman JD. Long-term exposure to air pollution and incidence of cardiovascular events in women. New England J Med. 2007;356:447–58. https://doi.org/10.1056/NEJMoa054409
48. Sin DD, Doiron D, Agusti A, Anzueto A, Barnes PJ, Celli BR, Criner GJ, Halpin D, Han MK, Martinez FJ, Montes de Oca M, Papi A, Pavord I, Roche N, Singh D, Stockley R, Lopez Varlera MV, Wedzicha J, Vogelmeier C, Bourbeau J. Air pollution and COPD: GOLD 2023 committee report. Eur Respir J. 2023;61:2202469. https://doi.org/10.1183/13993003.02469-2022
49. Wang M, Aaron CP, Madrigano J, Hoffman EA, Angelini E, Yang J, Laine A, Vetterli TM, Kinney PL, Sampson PD, Sheppard LE, Szpiro AA, Adar SD, Kirwa K, Smith B, Lederer DJ, Diez-Roux AV, Vedal S, Kaufman JD, Barr RG. Association between long-term exposure to ambient air pollution and change in quantitatively assessed emphysema and lung function. JAMA. 2019;322:546–56. https://doi.org/10.1001/jama.2019.10255
50. Doiron D, de Hoogh K, Probst-Hensch N, Fortier I, Cai Y, De Matteis S, Hansell AL. Air pollution, lung function and COPD: results from the population-based UK biobank study. Eur Respir J. 2019;54(1):1802140. https://doi.org/10.1183/13993003.02140-2018
51. Zanobetti A, O'Neill MS, Gronlund CJ, Schwartz JD. Summer temperature variability and long-term survival among elderly people with chronic disease. Proc Nat Acad Sci. 2012;109:6608–13. https://doi.org/10.1073/pnas.1113070109
52. Schwartz J. Who is sensitive to extremes of temperature?: A case-only analysis. Epidemiology. 2005;16:67–72. https://doi.org/10.1097/01.ede.0000147114.25957.71
53. Hansel NN, McCormack MC, Kim V. The effects of air pollution and temperature on COPD. COPD. 2016;13:372–9. https://doi.org/10.3109/15412555.2015.1089846
54. Donaldson GC, Seemungal T, Jeffries D, Wedzicha J. Effect of temperature on lung function and symptoms in chronic obstructive pulmonary disease. Eur Respir J. 1999;13:844–9. https://doi.org/10.1034/j.1399-3003.1999.13d25.x
55. Lin S, Luo M, Walker RJ, Liu X, Hwang SA, Chinery R. Extreme high temperatures and hospital admissions for respiratory and cardiovascular diseases. Epidemiology. 2009;20:738–46. https://doi.org/10.1097/EDE.0b013e3181ad5522
56. Anderson GB, Dominici F, Wang Y, McCormack MC, Bell ML, Peng RD. Heat-related emergency hospitalizations for respiratory diseases in the Medicare population. Am J Respir Crit Care Med. 2013;187:1098–103. https://doi.org/10.1164/rccm.201211-1969OC
57. Gutierrez MP, Zuidema P, Mirsaeidi M, Campos M, Kumar N. Association between African dust transport and acute exacerbations of COPD in Miami. J Clin Med. 2020;9:2496. https://doi.org/10.3390/jcm9082496
58. Tseng CM, Chen YT, Ou SM, Hsiao YH, Li SY, Wang SJ, Yang AC, Chen TJ, Perng DW. The effect of cold temperature on increased exacerbation of chronic obstructive pulmonary disease: a nationwide study. PLoS One. 2013;8:e57066. https://doi.org/10.1371/journal.pone.0057066
59. Sack C, Vedal S, Sheppard L, Raghu G, Barr RG, Podolanczuk A, Doney B, Hoffman EA, Gassett A, Hinckley-Stukovsky K, Williams K, Kawut S, Lederer DJ, Kaufman JD. Air pollution and subclinical interstitial lung disease: the Multi-Ethnic study of atherosclerosis (MESA) air-lung study. Eur Respir J. 2017;50:1700559. https://doi.org/10.1183/13993003.00559-2017
60. Rice MB, Li W, Schwartz J, Di Q, Kloog I, Koutrakis P, Gold DR, Hallowell RW, Zhang C, O'Connor G, Washko GR, Hunninghake GM, Mittleman MA. Ambient air pollution exposure and risk and progression of interstitial lung abnormalities: the framingham heart study. Thorax. 2019;74:1063–9. https://doi.org/10.1136/thoraxjnl-2018-212877
61. Conti S, Harari S, Caminati A, Zanobetti A, Schwartz JD, Bertazzi PA, Cesana G, Madotto F. The association between air pollution and the incidence of idiopathic pulmonary fibrosis in Northern Italy. Eur Respir J. 2018;51:1700397. https://doi.org/10.1183/13993003.00397-2017
62. Johannson KA, Vittinghoff E, Lee K, Balmes JR, Ji W, Kaplan GG, Kim DS, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. Eur Respir J. 2014;43:1124–31. https://doi.org/10.1183/09031936.00122213
63. Sesé L, Nunes H, Cottin V, Sanyal S, Didier M, Carton Z, Israel-Biet D, Crestani B, Cadranel J, Wallaert B, Tazi A, Maître B, Prévot G, Marchand-Adam S, Guillot-Dudoret S, Nardi A, Dury S, Giraud V, Gondouin A, Juvin K, Borie R, Wislez M, Valeyre D, Annesi-Maesano I. Role of atmospheric pollution on the natural history of idiopathic pulmonary fibrosis. Thorax. 2018;73:145–50. https://doi.org/10.1136/thoraxjnl-2017-209967

64. Aguilar PM, Carrera LG, Segura CC, Sánchez MIT, Peña MFV, Hernán GB, Rodríguez IE, Zapata RMR, Lucas EZD, Álvarez PDA, Bueno EV, Sánchez CP, Walther RÁS. Relationship between air pollution levels in Madrid and the natural history of idiopathic pulmonary fibrosis: severity and mortality. J Int Med Res. 2021;49:030006052110290. https://doi.org/10.1177/03000605211029058
65. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Hamid AM, Jaïs X, Simonneau G. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011;124:1973–81. https://doi.org/10.1161/CIRCULATIONAHA.110.015008
66. Swinnen K, Bijnens E, Casas L, Nawrot TS, Delcroix M, Quarck R, Belge C. Residential air pollution increases the risk for persistent pulmonary hypertension after pulmonary endarterectomy. Eur Respir J. 2021;57:2002680. https://doi.org/10.1183/13993003.02680-2020
67. de Miguel-Diez J, Blasco-Esquivias I, Rodriguez-Matute C, Bedate-Diaz P, Lopez-Reyes R, Fernandez-Capitan C, Garcia-Fuika S, Lobo-Beristain JL, Garcia-Lozaga A, Quezada CA, Murga-Arizabaleta I, Garcia-Ortega A, Rodríguez-Davila A, Marin-Barrera L, Otero-Candelera R, Praena-Fernandez JM, Jara-Palomares L. Correlation between short-term air pollution exposure and unprovoked lung embolism. prospective observational (Contamina-TEP Group). Thrombo Res. 2020;192:134–40. https://doi.org/10.1016/j.thromres.2020.04.033
68. Li Z, Zhang Y, Yuan Y, Yan J, Mei Y, Liu X, Xu Q, Shi J. Association between exposure to air pollutants and the risk of hospitalization for pulmonary embolism in Beijing, China: a case-crossover design using a distributed lag nonlinear model. Environm Res. 2022;204:112321. https://doi.org/10.1016/j.envres.2021.112321
69. Spiezia L, Campello E, Bon M, Maggiolo S, Pelizzaro E, Simioni P. Short-term exposure to high levels of air pollution as a risk factor for acute isolated pulmonary embolism. Thrombosis Res. 2014;134:259–63. https://doi.org/10.1016/j.thromres.2014.05.011
70. Leary PJ, Kaufman JD, Barr RG, Bluemke DA, Curl CL, Hough CL, Lima JA, Szpiro AA, Van Hee VC, Kawut SM. Traffic-related air pollution and the right ventricle. Am J Respir Crit Care Med. 2014;189:1093–100. https://doi.org/10.1164/rccm.201312-2298OC
71. Aaron CP, Chervona Y, Kawut SM, Roux AVD, Shen M, Bluemke DA, Van Hee VC, Kaufman JD, Barr RG. Particulate matter exposure and cardiopulmonary differences in the Multi-Ethnic study of atherosclerosis. Environ Health Perspect. 2016;124:1166–73. https://doi.org/10.1289/ehp.1409451
72. D'Souza JC, Kawut SM, Elkayam LR, Sheppard L, Thorne PS, Jacobs DR, Bluemke DA, Lima JAC, Kaufman JD, Larson TV, Adar SD. Ambient coarse particulate matter and the right ventricle: the Multi-Ethnic study of atherosclerosis. Environm Health Perspect. 2017;125(7):077019. https://doi.org/10.1289/EHP658
73. Marfella R, Prattichizzo F, Sardu C, Fulgenzi G, Graciotti L, Spadoni T, D'Onofrio N, Scisciola L, La Grotta R, Frigé C, Pellegrini V, Municinò M, Siniscalchi M, Spinetti F, Vigliotti G, Vecchione C, Carrizzo A, Accarino G, Squillante A, Spaziano G, Mirra D, Esposito R, Altieri S, Falco G, Fenti A, Galoppo S, Canzano S, Sasso FC, Matacchione G, Olivieri F, Ferraraccio F, Panarese I, Paolisso P, Barbato E, Lubritto C, Balestrieri ML, Mauro C, Caballero AE, Rajagopalan S, Ceriello A, D'Agostino B, Iovino P, Paolisso G. Microplastics and nanoplastics in atheromas and cardiovascular events. New England J Med. 2024;390(10):900–10. https://doi.org/10.1056/NEJMoa2309822
74. Baccini M, Biggeri A, Accetta G, Kosatsky T, Katsouyanni K, Analitis A, Anderson HR, Bisanti L, D'Ippoliti D, Danova J, Forsberg B, Medina S, Paldy A., Rabczenko D, Schindler C, Michelozzi P. Heat effects on mortality in 15 european cities. Epidemiology. 2008;19:711–9. https://doi.org/10.1097/EDE.0b013e318176bfcd
75. Costa-Beber LC, Guma FTCR. The macrophage senescence hypothesis: the role of poor heat shock response in pulmonary inflammation and endothelial dysfunction following chronic exposure to air pollution. Inflammat Res. 2022;71:1433–48. https://doi.org/10.1007/s00011-022-01647-2
76. Grunig G, Marsh LM, Esmaeil N, Jackson K, Gordon T, Reibman J, Kwapiszewska G, Park SH. Perspective: ambient air pollution: inflammatory response and effects on the lung's vasculature. Pulmon Circ. 2014;4:25–35. https://doi.org/10.1086/674902
77. Rabinovitch M, Guignabert C, Humbert M, Nicolls MR. Inflammation and immunity in the pathogenesis of pulmonary arterial hypertension. Circ Res. 2014;115:165–75. https://doi.org/10.1161/CIRCRESAHA.113.301141
78. Boucherat O, Peterlini T, Bourgeois A, Nadeau V, Breuils-Bonnet S, Boilet-Molez S, Potus F, Meloche J, Chabot S, Lambert C, Tremblay E, Chae YC, Altieri DC, Sutendra G, Michelakis ED, Paulin R, Provencher S, Bonnet S. Mitochondrial HSP90 accumulation promotes vascular remodeling in pulmonary arterial hypertension. American J Respir Critical Care Med. 2018;198:90–103. https://doi.org/10.1164/rccm.201708-1751OC
79. Wang GK, Li SH, Zhao ZM, Liu SX, Zhang GX, Yang F, Wang Y, Wu F, Zhao XX, Xu ZY. Inhibition of heat shock protein 90 improves pulmonary arteriole remodeling in pulmonary arterial hypertension. Oncotarget. 2016;7:54263–73. https://doi.org/10.18632/oncotarget.10855
80. Figgs LW. Increased pulmonary circulatory disease diagnosis risk associated with heatwave. J Clim Chan Health. 2022;5:100100. https://doi.org/10.1016/j.joclim.2021.100100
81. Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, Jing ZC, Gibbs JSR. A global view of pulmonary hypertension. Lancet Respir Med. 2016;4:306–22. https://doi.org/10.1016/S2213-2600(15)00543-3
82. De Leo GA, Stensgaard A-S, Sokolow SH. Schistosomiasis and climate change. BMJ. 2020. https://doi.org/10.1136/bmj.m4324

83. Huluka DK, Mekonnen D, Abebe S, Meshesha A, Mekonnen D, Deyessa N, Klinger JR, Ventetuolo CE, Schluger NW, Sherman CB, Amogne W. Prevalence and risk factors of pulmonary hypertension among adult patients with HIV infection in Ethiopia. Pulm Circu. 2020;10:1–6. https://doi.org/10.1177/2045894020971518
84. Lieber M, Chin-Hong P, Whittle HJ, Hogg R, Weiser SD. The synergistic relationship between climate change and the HIV/AIDS epidemic: a conceptual framework. AIDS Behav. 2021;25:2266–77. https://doi.org/10.1007/s10461-020-03155-y
85. Boyd R, McMullen H, Beqaj H, Kalfa D. Environmental exposures and congenital heart disease. Pediatrics. 2022;149:149. https://doi.org/10.1542/peds.2021-052151
86. Donnelly MC, Stableforth W, Krag A, Reuben A. The negative bidirectional interaction between climate change and the prevalence and care of liver disease: a joint BSG, BASL, EASL, and AASLD commentary. J Hepatol. 2022;76:995–1000. https://doi.org/10.1016/j.jhep.2022.02.012
87. Barragan-Martinez C, Speck-Hernandez CA, Montoya-Ortiz G. Organic solvents as risk factor for autoimmune diseases: a systematic review and meta-analysis. PLoS One. 2012;7:e51506. https://doi.org/10.1371/journal.pone.0051506
88. Aryal BK, Khuder SA, Schaub EA. Meta-analysis of systemic sclerosis and exposure to solvents. Am J Ind Med. 2001;40:271–4. https://doi.org/10.1002/ajim.1098
89. Marie I, Gehanno JF, Bubenheim M, Duval-Modeste AB, Joly P, Dominique S, Bravard P, Noël D, Cailleux AF, Weber J, Lagoutte P, Benichou J, Levesque H. Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature. Autoimm Rev. 2014;13:151–6. https://doi.org/10.1016/j.autrev.2013.10.002
90. Ruiz-Irastorza G, Garmendia M, Villar I, Egurbide MV, Aguirre C. Pulmonary hypertension in systemic lupus erythematosus: prevalence, predictors and diagnostic strategy. Autoimm Rev. 2013;12:410–5. https://doi.org/10.1016/j.autrev.2012.07.010
91. Barr WG, Fahey PJ. Reduction of pulmonary capillary blood volume following cold exposure in patients with raynaud's phenomenon. Chest. 1988;94:1195–9. https://doi.org/10.1378/chest.94.6.1195
92. Noyes PD, McElwee MK, Miller HD, Clark BW, Van Tiem LA, Walcott KC, Erwin KN, Levin ED. The toxicology of climate change: environmental contaminants in a warming world. Environ Int. 2009;35:971–86. https://doi.org/10.1016/j.envint.2009.02.006
93. UKHSA. Health Effects of Climate Change in the UK: 2023 report. Chapter 12. Impact of climate change on human exposure to chemicals in the UK. UKHSA; 2023.
94. Haque A, Kiely DG, Kovacs G, Thompson AAR, Condliffe R. Pulmonary hypertension phenotypes in patients with systemic sclerosis. Euro Respir Rev. 2021;30:210053. https://doi.org/10.1183/16000617.0053-2021
95. Van Hee VC, Adar SD, Szpiro AA, Barr RG, Bluemke DA, Diez Roux AV, Gill EA, Sheppard L, Kaufman JD. Exposure to traffic and left ventricular mass and function: the Multi-Ethnic study of atherosclerosis. American J Respir Crit Care Med. 2009;179:827–34. https://doi.org/10.1164/rccm.200808-1344OC
96. Van Zutphen AR, Hsu WH, Lin S. Extreme winter temperature and birth defects: a population-based case-control study. Environ Res. 2014;128:1–8. https://doi.org/10.1016/j.envres.2013.11.006
97. Bois JP, Adams JC, Kumar G, Ommen SR, Nishimura RA, Klarich KW. Relation between temperature extremes and symptom exacerbation in patients with hypertrophic cardiomyopathy. American J Cardiol. 2016;117:961–5. https://doi.org/10.1016/j.amjcard.2015.12.046
98. Redfors B, Simonato M, Chen S, Vincent F, Zhang Z, Thiele H, Eitel I, Patel MR, Ohman EM, Maehara A, Ben-Yehuda O, Stone GW. Ambient temperature and infarct size, microvascular obstruction, left ventricular function and clinical outcomes after ST-segment elevation myocardial infarction. Coron Artery Dis. 2022;33:81–90. https://doi.org/10.1097/MCA.0000000000001099
99. Egbe AC, Miranda WR, Connolly HM, Borlaug BA. Coarctation of aorta is associated with left ventricular stiffness, left atrial dysfunction and pulmonary hypertension. American Heart J. 2021;241:50–8. https://doi.org/10.1016/j.ahj.2021.07.005
100. Ahmed EA, Schaff HV, Al-Lami HS. Prevalence and influence of pulmonary hypertension in patients with obstructive hypertrophic cardiomyopathy undergoing septal myectomy. J Thorac Cardiovasc Surg. 2022;20220907. https://doi.org/10.1016/j.jtcvs.2022.08.023
101. Harari S, Raghu G, Caminati A. Fibrotic interstitial lung diseases and air pollution: a systematic literature review. Eur Respir Rev. 2020:29. https://doi.org/10.1183/16000617.0093-2020
102. Hou T, Zhang J, Wang Y, Zhang G, Li S, Fan W, Li R, Sun Q, Liu C. Early pulmonary fibrosis-like changes in the setting of heat exposure: DNA damage and cell senescence. Int J Mol Sci. 2024;25:2992. https://doi.org/10.3390/ijms25052992
103. Kharwadkar S, Attanayake V, Duncan J, Navaratne N., Benson J. The impact of climate change on the risk factors for tuberculosis: A systematic review. Environ Res. 2022;212:113436. https://doi.org/10.1016/j.envres.2022.113436
104. van Heerden JK, Louw EH, Thienemann F, Engel ME, Allwood BW. The prevalence of pulmonary hypertension in post-tuberculosis and active tuberculosis populations: a systematic review and meta-analysis. Euro Respir Rev. 2024;33:230154. https://doi.org/10.1183/16000617.0154-2023
105. Kulp SA, Strauss BH. New elevation data triple estimates of global vulnerability to sea-level rise and coastal flooding. Nat Commun. 2019;10:4844. https://doi.org/10.1038/s41467-019-12808-z
106. Maggiorini M, Leon-Velarde F. High-altitude pulmonary hypertension: a pathophysiological entity to different diseases. Eur Respir J. 2003;22:1019–25. https://doi.org/10.1183/09031936.03.00052403
107. Adir Y, Humbert M, Chaouat A. Sleep-related breathing disorders and pulmonary hypertension. Eur Respir J.

2021;57:2002258. https://doi.org/10.1183/13993003.02258-2020

108. Swinburn BA, Kraak VI, Allender S, Atkins VJ, Baker PI, Bogard JR, Brinsden H, Calvillo A, De Schutter O, Devarajan R, Ezzati M, Friel S, Goenka S, Hammond RA, Hastings G, Hawkes C, Herrero M, Hovmand PS, Howden M, Jaacks LM, Kapetanaki AB, Kasman M, Kuhnlein HV, Kumanyika SK, Larijani B, Lobstein T, Long MW, Matsudo VKR, Mills SDH, Morgan G, Morshed A, Nece PM, Pan A, Patterson DW, Sacks G, Shekar M, Simmons GL, Smit W, Tootee A, Vandevijvere S, Waterlander WE, Wolfenden L, Dietz WH. The global syndemic of obesity, undernutrition, and climate change: the lancet commission report. Lancet. 2019;393:791–846 https://doi.org/10.1016/S0140-6736(18)32822-8
109. Franchini M, Mengoli C, Cruciani M, Bonfanti C, Mannucci PM. Association between particulate air pollution and venous thromboembolism: a systematic literature review. Euro J Int Med. 2016;27:10–3. https://doi.org/10.1016/j.ejim.2015.11.012
110. Quarck R, Wynants M, Verbeken E, Meyns B., Delcroix M. Contribution of inflammation and impaired angiogenesis to the pathobiology of chronic thromboembolic pulmonary hypertension. Eur Respir J. 2015;46:431–43. https://doi.org/10.1183/09031936.00009914
111. Aung N, Sanghvi MM, Zemrak F, Lee AM, Cooper JA, Paiva JM, Thomson RJ, Fung K, Khanji MY, Lukaschuk E, Carapella V, Kim YJ, Munroe PB, Piechnik SK, Neubauer S, Petersen SE. Association between ambient air pollution and cardiac Morpho-Functional phenotypes: insights from the UK biobank population imaging study. Circulation. 2018;138:2175–86. https://doi.org/10.1161/CIRCULATIONAHA.118.034856
112. Green DJ, Maiorana AJ, Siong JHJ, Burke V, Erickson M, Minson CT, Bilsborough W, O'Driscoll G. Impaired skin blood flow response to environmental heating in chronic heart failure. Eur Heart J. 2006;27:338–43. https://doi.org/10.1093/eurheartj/ehi655
113. Cui J, Arbab-Zadeh A, Prasad A, Durand S, Levine BD, Crandall CG. Effects of heat stress on thermoregulatory responses in congestive heart failure patients. Circulation. 2005;112:2286–92. https://doi.org/10.1161/CIRCULATIONAHA.105.540773
114. Kitamura Y, Nakai H. Maintaining quality of life and care for cancer survivors experiencing disaster disruptions: a review of the literature. BMC Cancer. 2023;23:701. https://doi.org/10.1186/s12885-023-11191-9
115. Chen G, Guo Y, Yue X, Tong S, Gasparrini A, Bell ML, Armstrong B, Schwartz J, Jaakkola JJK, Zanobetti A, Lavigne E, Nascimento Saldiva PH, Kan H, Royé D, Milojevic A, Overcenco A, Urban A, Schneider A, Entezari A, Vicedo-Cabrera AM, Zeka A, Tobias A, Nunes B, Alahmad B, Forsberg B, Pan SC, Íñiguez C, Ameling C, De la Cruz Valencia C, Åström C, Houthuijs D, Van Dung D, Samoli E, Mayvaneh F, Sera F, Carrasco-Escobar G, Lei Y, Orru H, Kim H, Holobaca IH, Kyselý J, Teixeira JP, Madureira J, Katsouyanni K, Hurtado-Díaz M, Maasikmets M, Ragettli MS, Hashizume M, Stafoggia M, Pascal M, Scortichini M, de Sousa Zanotti Stagliorio Coêlho M, Valdés Ortega N, Ryti NRI, Scovronick N, Matus P, Goodman P, Garland RM, Abrutzky R, Garcia SO, Rao S, Fratianni S, Dang TN, Colistro V, Huber V, Lee W, Seposo X, Honda Y, Guo YL, Ye T, Yu W, Abramson MJ, Samet JM, Li S. Mortality risk attributable to wildfire-related PM(2.5) pollution: a global time series study in 749 locations. Lancet Planet Health. 2021;5:e579–87. https://doi.org/10.1016/S2542-5196(21)00200-X
116. Elliot AJ, Hughes HE, Hughes TC, Locker TE, Brown R, Sarran C, Clewlow Y, Murray V, Bone A, Catchpole M, McCloskey B, Smith GE. The impact of thunderstorm asthma on emergency department attendances across London during July 2013. Emerg Med J. 2014;31:675–8. https://doi.org/10.1136/emermed-2013-203122
117. He C, Chen R, Kim H, Hashizume M, Lee W, Honda Y, Kim SE, Guo YL, Schneider A, Ge W, Zhu Y, Zhou L, Kan H. Tropical cyclone and daily respiratory mortality across east Asia: a time series study. Eur Respir J. 2023;62:2300546. https://doi.org/10.1183/13993003.00546-2023
118. Rosenthal A, Stover E, Haar RJ. Health and social impacts of california wildfires and the deficiencies in current recovery resources: an exploratory qualitative study of systems-level issues. PLoS One. 2021;16:e0248617. https://doi.org/10.1371/journal.pone.0248617
119. Jenkins JL, Hsu EB, Sauer LM, Hsieh YH, Kirsch TD. Prevalence of unmet health care needs and description of health care-seeking behavior among displaced people after the 2007 california wildfires. Disas Med Pub Health Prepare. 2009;3:S24–8. https://doi.org/10.1097/DMP.0b013e31819f1afc
120. Sahota H, Guzman S, Tordera L, Chan M., Cocohoba J., Saberi P. Pharmacy deserts and pharmacies' roles Post-Extreme weather and climate events in the United States: A scoping review. J Prim Care Comm Health. 2023;14:21501319231186497. https://doi.org/10.1177/21501319231186497
121. Li X, Tan H, Li S, Zhou J, Liu A, Yang T, Wen SW, Sun Z. Years of potential life lost in residents affected by floods in hunan, China. Transact Royal Socf Tropical Med Hyg. 2007;101:299–304. https://doi.org/10.1016/j.trstmh.2006.05.011
122. Sagoschen I, Scibior B, Farmakis IT. A multidisciplinary pulmonary embolism response team (PERT): first experience from a single center in Germany. Clin Res Card. 2023;20231219. https://doi.org/10.1007/s00392-023-02364-4
123. Rocklöv J, Semenza JC, Dasgupta S, Robinson EJZ, Abd El Wahed A, Alcayna T, Arnés-Sanz C, Bailey M, Bärnighausen T, Bartumeus F, Borrell C, Bouwer LM, Bretonnière PA, Bunker A, Chavardes C, van Daalen KR, Encarnação J, González-Reviriego N, Guo J, Johnson K, Koopmans MPG, Máñez Costa M, Michaelakis A, Montalvo T, Omazic A, Palmer JRB, Preet R, Romanello M, Shafiul Alam M, Sikkema RS, Terrado M, Treskova M, Urquiza D, Lowe R, Rocklöv J, Guo J, Semenza JC, Preet R, Sjodin H, Farooq Z, Sewe M, Romanello M, MacGuire F, Michaelakis A, Zavitsanou E, Milonas P, Papachristos D, Bisia M, Balatsos G, Antonatos S,

Martinez-Urtaza J, Triñanes J, Encarnação J, Williams M, Palmer JRB, Dekramanjian B, Broome K, Johnson O, Bouwer L, Costa MM, Martin A, Kotova L, Wübbelmann T, Bunker A, Bärnighausen T, Walsh F, Treskova M, Stiles P, Baron J, Hatfield C, Heidecke J, Singh P, Dasgupta S, Johnson K, Bosello F, Robinson EJZ, Mehryar S, Alcayna T, Bailey M, Koopmans MPG, Sikkema RS, de Best P, Hartung T, Abourashed A, Bartumeus F, Bellver J, Cerecedo C, Lowe R, Bautista ML, Moreira de Carvalho B, Fletcher C, González-Reviriego N, Terrado M, Urquiza D, Bretonnière PA, Rosenbluth J, Corradini M, Ramon J, van Daalen KR, Brodie LP, Llabres A, El Wahed AA, Ceruti A, Truyen U, Chavardes C, Rodrigues S, Omazic A, Ågren E, Grandi G, Widgren S, Parvage M, Bergström M, Alam MS, Haque R, Khan WA, Montalvo T, Valsecchi A, Barahona L, Realp E, Borrell C, de Roode S. Decision-support tools to build climate resilience against emerging infectious diseases in Europe and beyond. The Lancet Regional Health - Europe. 2023;32:100701. https://doi.org/10.1016/j.lanepe.2023.100701

124. Lokmic-Tomkins Z, Bhandari D, Bain C, Borda A, Kariotis TC, Reser D. Lessons learned from natural disasters around digital health technologies and delivering quality healthcare. Int J Environm Res Pub Health. 2023;20:4542. https://doi.org/10.3390/ijerph20054542
125. Curtis S, Fair A, Wistow J, Val DV, Oven K. Impact of extreme weather events and climate change for health and social care systems. Environ Health. 2017;16:128. https://doi.org/10.1186/s12940-017-0324-3
126. Medtronic. Implantable system for remodulin SynchroMed II 8637P Pump, 8201 Catheter, and 8870 Application Card. 2017. accessed 30.01. 2024. https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140032C.pdf
127. Spruit MA, Pitta F, McAuley E, ZuWallack RL, Nici L. Pulmonary rehabilitation and physical activity in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015;192:924–33. https://doi.org/10.1164/rccm.201505-0929CI
128. Del Pozo Cruz B, Ahmadi MN, Lee IM, Stamatakis E. Prospective associations of daily step counts and intensity with cancer and cardiovascular disease incidence and mortality and all-cause mortality. JAMA Int Med. 2022;182:1139–48. https://doi.org/10.1001/jamainternmed.2022.4000
129. Fischer A, Johansson I, Blomberg A, Sundström B. Adherence to a Mediterranean-like diet as a protective factor against COPD: a nested Case-Control study. COPD. 2019;16:272–7. https://doi.org/10.1080/15412555.2019.1634039
130. Dybvik JS, Svendsen M, Aune D. Vegetarian and vegan diets and the risk of cardiovascular disease, ischemic heart disease and stroke: a systematic review and meta-analysis of prospective cohort studies. Euro J Nutr. 2023;62:51–69. https://doi.org/10.1007/s00394-022-02942-8
131. Ravindra K, Goyal A, Mor S. Lifestyle for environment (LiFE): a global initiative to fight against climate change through community engagement and lifestyle modification. Lancet Reg Health Southeast Asia. 2023;15:100238. https://doi.org/10.1016/j.lansea.2023.100238
132. Quam V., Rocklöv J, Quam M, Lucas R. Assessing greenhouse gas emissions and health co-benefits: a structured review of lifestyle-related climate change mitigation strategies. Int J Environm Res Pub Health. 2017;14:468. https://doi.org/10.3390/ijerph14050468
133. Josey KP, Delaney SW, Wu X, Nethery RC, DeSouza P, Braun D, Dominici F. Air pollution and mortality at the intersection of race and social class. New England J Med. 2023;388:1396–404. https://doi.org/10.1056/NEJMsa2300523
134. Cesaroni G, Boogaard H, Jonkers S, Porta D, Badaloni C, Cattani G, Forastiere F, Hoek G. Health benefits of traffic-related air pollution reduction in different socioeconomic groups: the effect of low-emission zoning in Rome. Occupat Environ Med. 2012;69:133–9. https://doi.org/10.1136/oem.2010.063750
135. Kodros JK, O'Dell K, Samet JM, L'Orange C, Pierce JR, Volckens J. Quantifying the health benefits of face masks and respirators to mitigate exposure to severe air pollution. Geohealth. 2021;5:e2021GH000482. https://doi.org/10.1029/2021GH000482
136. Hansel NN, Putcha N, Woo H, Peng R., Diette GB, Fawzy A, Wise RA, Romero K, Davis MF, Rule AM, Eakin MN, Breysse PN, McCormack MC, Koehler K. Randomized clinical trial of air cleaners to improve indoor air quality and chronic obstructive pulmonary disease health: results of the CLEAN AIR study. American J Respir Crit Care Med. 2022;205:421–30. https://doi.org/10.1164/rccm.202103-0604OC
137. Windfeld ES, Brooks MSL. Medical waste management—a review. J Environm Manag. 2015;163:98–108. https://doi.org/10.1016/j.jenvman.2015.08.013
138. Eckelman MJ, Sherman J. Environmental impacts of the U.S. health care system and effects on public health. PLoS One. 2016;11:e0157014. https://doi.org/10.1371/journal.pone.0157014
139. Wesley Milks M, Sahay S, Benza RL, Farber HW. Risk assessment in patients with pulmonary arterial hypertension in the era of COVID 19 pandemic and the telehealth revolution: state of the art review. J Heart Lung Transplant. 2021;40:172–82. https://doi.org/10.1016/j.healun.2020.12.005
140. Gonzalez-Garcia MC, Fatehi F, Varnfield M. Use of ehealth in the management of pulmonary arterial hypertension: review of the literature. BMJ Health Care Inform. 2020;:27. https://doi.org/10.1136/bmjhci-2020-100176
141. WHO. Factsheet: sustainable development goals: Health targets: Rehabilitation. 2019. Accessed 15.04. 2024. https://iris.who.int/bitstream/handle/10665/340896/WHO-EURO-2019-2384-42139-58051-eng.pdf?sequence=1
142. Grünig E, MacKenzie A, Peacock AJ, Eichstaedt CA, Benjamin N, Nechwatal R, Ulrich S, Saxer S, Bussotti M, Sommaruga M, Ghio S, Gumbiene L, Palevičiūtė E, Jurevičienė E, Cittadini A, Stanziola A., Marra AM, Kovacs G, Olschewski H, Barberà JA, Blanco I, Spruit MA, Franssen FME, Vonk Noordegraaf A, Reis A, Santos M, Viamonte SG, Demeyer H, Delcroix M, Bossone E, Johnson M. Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large european multicentre randomized controlled

trial. Eur Heart J. 2021;42:2284–95. https://doi.org/10.1093/eurheartj/ehaa696

143. McCormack C, Kehoe B, Hardcastle SJ, McCaffrey N, McCarren A, Gaine S, McCullagh B, Moyna N. Pulmonary hypertension and home-based (PHAHB) exercise intervention: protocol for a feasibility study. BMJ Open. 2021;11:e045460. https://doi.org/10.1136/bmjopen-2020-045460

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