Received: 8 February 2021 | Revised: 10 May 2021 | Accepted: 25 May 2021

DOI: 10.1002/bies.202100046

BioEssays

PROBLEMS & PARADIGMS

Prospects & Overviews

Air pollution and cardiovascular disease: Can the Australian bushfires and global COVID-19 pandemic of 2020 convince us to change our ways?

Kathryn Wolhuter[1] | **Manish Arora**[2] | **Jason C. Kovacic**[1,3,4]

[1] Victor Chang Cardiac Research Institute, Sydney, Australia

[2] Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[3] St Vincent's Clinical School, University of New South Wales, Sydney, Australia

[4] Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA

Correspondence
Jason C. Kovacic, Victor Chang Cardiac Research Institute, Lowy Packer Building, 405 Liverpool St, Darlinghurst, NSW 2010, Australia.
Email: j.kovacic@victorchang.edu.au

Funding information
National Institutes of Health, Grant/Award Numbers: R01HL130423, R01HL135093, R01HL148167-01A1; NSW Ministry of Health, Grant/Award Number: RG194194

Abstract

Air pollution is a major global challenge for a multitude of reasons. As a specific concern, there is now compelling evidence demonstrating a causal relationship between exposure to airborne pollutants and the onset of cardiovascular disease (CVD). As such, reducing air pollution as a means to decrease cardiovascular morbidity and mortality should be a global health priority. This review provides an overview of the cardiovascular effects of air pollution and uses two major events of 2020—the Australian bushfires and COVID-19 pandemic lockdown—to illustrate the relationship between air pollution and CVD. The bushfires highlight the substantial human and economic costs associated with elevations in air pollution. Conversely, the COVID-19-related lockdowns demonstrated that stringent measures are effective at reducing airborne pollutants, which in turn resulted in a potential reduction in cardiovascular events. Perhaps one positive to come out of 2020 will be the recognition that tough measures are effective at reducing air pollution and that these measures have the potential to stop thousands of deaths from CVD.

KEYWORDS
air pollution, bushfires, cardiovascular disease, COVID-19, PM10, PM2.5

INTRODUCTION

Air pollutants have measurable health impacts, with particularly profound effects on cardiovascular health. Ambient air pollution is the number one environmental risk factor for all-cause mortality, and ranks 5th overall, higher than tobacco smoking, HIV/AIDS, and all forms of violence including war.[1] An estimated 8.8 million excess deaths a year are attributable to poor air quality with an associated healthcare cost of US$1–3 trillion.[2,3] We cannot choose the air that we breathe and while air quality has improved in many developed countries since the 1970s, 90% of the world's population currently live in areas where air pollution exceeds World Health Organization's (WHO) guidelines, with a disproportionate percentage of those in developing countries. Worryingly, recent epidemiological evidence suggests that even air pollution levels below WHO guidelines are still associated with damaging health effects.[4,5]

Numerous epidemiological studies have correlated increased air pollution to a range of cardiovascular diseases (CVDs) including arrhythmias,[6,7] atherosclerosis[8] and acute myocardial infarction (AMI).[9] Despite the lungs being the major entry point of airborne pollutants into the body, 60% of deaths attributed to pollution are due to CVD, outweighing mortality due to respiratory disease.[1] These findings demonstrate that airborne pollutants play a key role in mediating CVD progression. With 30% of global CVD deaths currently attributable to air pollution, combatting poor air quality to reduce CVD morbidity should now be a global priority.

Here, we discuss the ways in which air pollution elicits its detrimental effects on the cardiovascular system and how two major events in

2020 drastically altered air pollution levels and their knock-on effects on CVD mortality. Using the Australian bushfires of 2019–2020 and the COVID-19 pandemic lockdown as examples, we consider the importance of reducing air pollution as a mechanism to combat CVD.

COMPOSITION AND SOURCES OF AIRBORNE POLLUTANTS

Air pollution is a heterogeneous mix of gases, semi-volatile liquids, and particles, the exact composition of which is dependent on pollutant sources and environmental factors. In general, these pollutants are classified into primary and secondary pollutants, formed via physico-chemical transformation of primary pollutants. Primary pollutants encompass particulate matter (PM), hydrocarbons, and inorganic gasses (e.g., ozone, nitrogen dioxide [NO_2], sulfur dioxide [SO_2]). Although negative correlations have been reported between gaseous pollutants, studies performed using isolation chambers found that ambient levels of these gases alone do not induce acute cardiovascular dysfunction.[10] It is proposed that instead of acting directly to induce CVD, gaseous pollutants can act as co-pollutants, amplifying the detrimental effects of PM.[11] Consequently, PM is currently considered to be the primary mediator of air pollutant-induced cardiovascular events and will be focused upon throughout this review.

Airborne PM is a mixture of solid and liquid particles of a variety of sizes suspended in the air. Particles are composed of various materials including, but not limited to, elemental or organic carbon, mineral dust, organic compounds (e.g., polycyclic aromatic hydrocarbons [PAHs]), biological material (e.g., cell fragments), metals (e.g., lead), and sea salt. Primary particles can react with gases in the atmosphere resulting in secondary PM formed of a core surrounded by a variety of chemical compounds. The availability of chemicals on the surface of particles changes their ability to induce pathological responses, and the cardiovascular effects of PM are highly dependent on their source. Urban PM has been linked to multiple cardiac effects while rural PM increased blood pressure. However, maritime wind PM was observed to have no adverse cardiac effects.[12] PM can also absorb biological material, such as endotoxins or viruses, enhancing pathogenicity.[13]

Due to the complex nature of PM, it is typically classified by the size of the particles (Figure 1A). Coarse particles have a diameter of 2.5–10 μm (PM_{10}), and 10 of these particles could comfortably sit across the width of a human hair, making them small enough to deposit in the tracheobronchial tree of the lung. They are produced by sources including bushfires, road dust, agriculture, and sea spray. These particles are commonly comprised of dust, pollen, metals (e.g., silicone, aluminium), and ground materials. PM_{10} has a half-life of hours to days and are distributed up to 100 km from their source. Current WHO guidelines recommend that average daily exposure to PM_{10} is kept below 50 μg per cubic meter of air (μg/m^3). An elevation in PM_{10} of 10 μg/m^3 is estimated to increase daily cardiopulmonary mortality by 0.68%.[14]

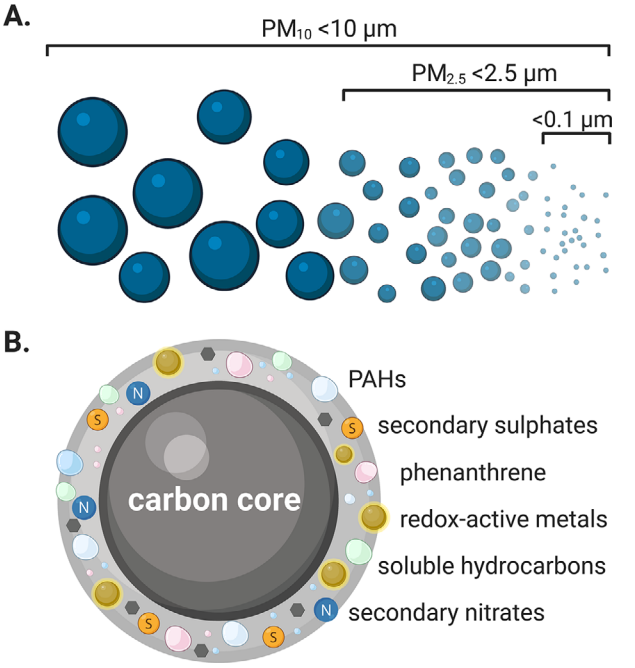

FIGURE 1 Composition of particulate matter (PM) in air pollution. (A) Particles with a diameter of 2.5–10 μm are classified as coarse particles (PM10). Fine particles have a diameter of 0.1–2.5 μm (PM2.5) and ultrafine particles have a diameter less than 0.1 μm. (B) PM2.5 derived from combustion have a complex composition typically with an elemental carbon core coated with a range of chemical species including polycyclic aromatic hydrocarbons (PAHs), reactive metals, and secondary sulfate or nitrate compounds. The exact composition of PMs is determined by their source and the local environment. *Figure 1 not to scale*

Particles with a diameter of 0.1–2.5 μm are defined as fine particles or $PM_{2.5}$. These particles are typically carbon-based and are the major product of combustion from sources including vehicle engines, coal power plants, and bushfires. Primary $PM_{2.5}$ readily form secondary particles with a coat of constituents including ions (e.g., nitrates, sulfates), redox-active metals (e.g., copper, iron) and PAH (Figure 1B). These fine particles can travel ~1000 km away from their source with a half-life of up to a week, allowing them to exert their effects over vast areas. Their small size provides a relatively large reactive surface area and allows for penetration deep into the lungs to reach the alveoli, thereby increasing their toxicity. WHO guidelines recommend $PM_{2.5}$ exposure should average below 25 μg/m^3 over 24 h. Numerous epidemiological studies have correlated elevations in $PM_{2.5}$ with an increased risk of cardiovascular events, as previously reviewed.[15] Short-term elevations in daily $PM_{2.5}$ exposure by 10 μg/m^3 have been found to increase daily CVD mortality by up to 2%.[16,17]

Currently, only $PM_{2.5}$ and PM_{10} levels are detected by most monitoring stations; however, there is a third class known as ultrafine PM with a diameter of less than 0.1 μm. Ultrafine particles are similar in composition to $PM_{2.5}$ and are primarily composed of organic carbon, hydrocarbons, and metals. These particles are of particular interest as they can deposit deep within the alveoli.[18] They also have the potential to pass directly into the circulatory system resulting in systemic

dissemination and enhanced biological toxicity.[19,20] However, as they tend to coalesce into larger particles, they have a relatively short half-life. Due to the abundance of ultrafine particles from vehicle exhaust and their potential to induce higher degree adverse effects, there are concerns that current methods to measure air quality rely only on PM_{10} and $PM_{2.5}$ are oversimplistic, resulting in researchers overlooking the importance of ultrafine particles in CVD progression.

THE CARDIOMETABOLIC EFFECTS OF AIR POLLUTANTS

Extensive epidemiological studies have correlated air pollution to various CVDs, including atherosclerosis,[21] venous thrombosis,[22] stroke,[23] arrhythmia,[24] cardiac arrest[25] and heart failure.[10] Both acute and long-term exposure to pollutants, particularly PM, are correlated with CVD mortality. Epidemiological studies, along with work performed in small animals and humans, illustrate the ability of airborne pollutants to impinge on almost all aspects of cardiovascular function. While the effects of air pollution are extensive and have been reviewed in detail elsewhere,[26–28] below is a brief overview of the effects upon the vasculature and heart.

Vascular disease

Exposure to air pollution is associated with increased blood pressure predominantly due to altered vascular function.[29,30] Human studies revealed that PM in diesel exhaust promotes vasoconstriction and decreases vasorelaxation in response to agonists. In apolipoprotein E knockout mice (a model of atherosclerosis), long-term exposure to $PM_{2.5}$ resulted in altered vascular tone and increased the accumulation of oxidised lipids, which together potentiated atherosclerosis.[31] It is proposed that $PM_{2.5}$ impairs high-density lipoprotein function leading to increased plaque burden. Additionally, PM may facilitate the transition of plaques from a stable to unstable phenotype with an increased risk of plaque rupture.[32] These findings emphasize the ability of airborne pollutants to induce vascular dysfunction and accelerate the progression of vascular disease.

Cerebrovascular disease

Several meta-analyses and other studies have demonstrated a robust association between both gaseous and PM pollution with stroke hospital admissions and mortality.[23,33] A recent study into long-term exposure to differing levels of $PM_{2.5}$ in cities across China found that with each 10 $\mu g/m^3$ increase in $PM_{2.5}$ there was a 13% increase in stroke incidence, with the most notable increase observed in ischemic stroke, which had a 20% increase in presentations per 10 $\mu g/m^3$ increase in $PM_{2.5}$.[34] Additionally, short-term elevations in multiple gaseous pollutants correlate with a significant increase in ischemic stroke mortality. Elevations in ozone were linked to an increase in stroke mortality 3-days post-exposure whereas elevated CO and NO_2 levels increase stroke mortality in the following 24 h.[35] These studies highlight the acute and varying effects of different air pollutants on the cerebrovascular system. Air pollutant-induced stoke events are exacerbated in patients with a history of stoke,[36] demonstrating the detrimental effects of airborne pollutants in at-risk populations.

Cardiac disease

Long-term exposure to air pollution is ranked in the top 10 risk factors for ischemic heart disease, placing it above the impact of a sedentary lifestyle (lack of exercise).[37] $PM_{2.5}$, NO_2, and ozone have all been associated with AMI, with $PM_{2.5}$ having a near-linear concentration-response relationship to the disease.[38] Air pollution can rapidly induce cardiac events with acute exposure to traffic-derived pollutants increasing the risk of AMI in the following 2 h.[39,40] Elevated risk of AMI in response to traffic-derived pollutants was shown to be independent of the mode of transport or level of physical exercise.

The effects of pollutants are exacerbated in vulnerable individuals predisposed to cardiac problems, with reduced heart rate variability (HRV) being one example of this. While exposure to air pollution is associated with reduced HRV,[41] these effects were potentiated and occurred upon exposure to a lower concentration of pollutants in elderly individuals.[42] Preclinical studies found that pollutant-induced reduced HRV is associated with increased risk of arrhythmias and delayed cardiac conductance with long-term exposure resulting in cardiac hypertrophy and loss of cardiac function.[43–45]

MECHANISMS OF POLLUTANT-INDUCED CVD

The precise mechanisms by which airborne pollutants elicit their effects on the cardiovascular system are still largely unknown. It is proposed that pollutants elicit direct effects on the cardiovascular system as well as indirect effects via epigenetic changes, inflammatory responses, and other mechanisms (Figure 2). The combined effects of air pollution stimulate pathological processes including endothelial damage, vascular dysfunction, autonomic and neuroendocrine dysfunction, thrombosis, and atherosclerosis.

One mechanism by which inhaled pollutants are proposed to alter cardiovascular function is via direct activation of alveolar receptors that alter neuroendocrine signaling and autonomic balance.[46,47] Reduced HRV in response to PM exposure results from changes in the autonomic nervous system with increased sympathetic activity and reduced parasympathetic activity.[48] PAHs present on the surface of PM appears to be a key driver in activating sensory neurons.[49]

The soluble fraction of PM and ultrafine PM (<30 nm) may pass through into the bloodstream resulting in direct systemic effects on the vasculature. Iron-based particles have been identified in the hearts and brains of cadavers from Mexico City, which is known for high air pollution.[50,51] The presence of these particles was associated with cellular damage in the surrounding tissues. Recent human studies

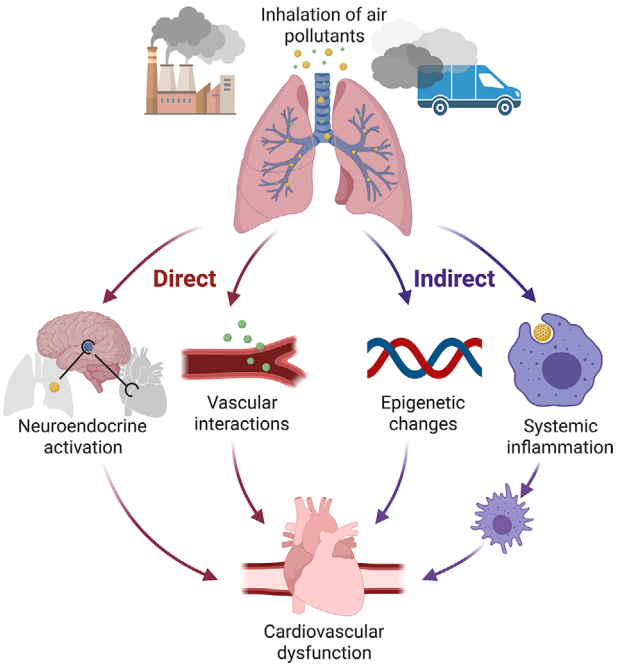

FIGURE 2 Proposed mechanisms of cardiovascular damage induced by inhaled airborne pollutants. The direct effects of airborne pollutants include changes to neuroendocrine signaling and direct vascular interactions that alter cardiac function. Pollutants can induce epigenetic changes with downstream effects on the cardiovascular system. They also activate inflammatory cells in the lungs, including macrophages, leading to systemic inflammation and potentiation of oxidative stress leading to cardiac dysfunction

utilizing inhaled 5 nm gold particles demonstrated that particles could persist within the circulatory system for up to 3 months. Furthermore, once particles enter the circulatory system, they preferentially accumulate in atherosclerosis-prone arteries.[52] Build-up of PM around an atherosclerotic lesion may elevate oxidative stress and inflammation in the area, consequently accelerating disease progression.

Air pollutants induce additional indirect effects on the cardiovascular system via inflammatory agents, oxidative stress, and epigenetic changes. Macrophages and other inflammatory cells present within the lining of the alveoli can phagocytose inhaled pollutants, as they would other invading pathogens. The physico-chemical properties of PM derived from combustion sources promote activation of inflammatory cells leading to local and systemic inflammation.[53] The activation of inflammatory cells has the potential to amplify the detrimental effects of PM via the release of inflammatory mediators that pass into the circulation and induce marked changes in other cells, including endothelial cells, thereby altering cardiovascular function.[54] As well as inflammatory markers, oxidative stress markers are also consistently elevated in the blood after exposure to PM.[55–57] Pollutants induce oxidative stress via mechanisms including PM-mediated free radical generation, oxidant production from pollutant-activated immune cells, and indirect activation of intracellular oxidant-producing enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[58] Current research has identified a clear role for oxidative stress in governing CVD progression.

There is mounting evidence that airborne pollutants can indirectly influence cardiac homeostasis through epigenetic changes. A recent animal study demonstrated that exposure to $PM_{2.5}$ altered chromatin accessibility causing dysregulation of multiple cardiometabolic pathways.[59] Sustained exposure of mice to $PM_{2.5}$ resulted in impaired glucose and insulin tolerance associated with differential expression of gene clusters involved with metabolism, circadian rhythm, and inflammation. It is postulated that exposure to PM alters DNA methylation in genes governing inflammation, cytokine production, and endothelial dysfunction, all of which contribute to pollutant-induced CVD.[60,61] Interestingly, changes in response to $PM_{2.5}$ were transient with the cessation of exposure resulting in a reversal of insulin resistance.[59]

The ability of air pollutants to induce complex direct and indirect effects is exemplified by studies on diesel exhaust. Acute exposure to diesel exhaust impairs vasorelaxation in response to vasodilators in human studies, suggesting direct impairment of NO-mediated vasorelaxation.[62] The effects on the vasculature were found to be rapidly induced (1–2 h), and these effects could persist for up to 24 h.[63] Diesel exhaust has been shown to directly activate platelets that promoted blood clotting in an *ex vivo* thrombosis model.[64] In addition to these direct effects, PM from diesel fumes induces indirect oxidative stresses and alters redox signaling in multiple cardiovascular systems.[58] Diesel PM has been shown to generate superoxide and hydroxyl free radicals,[65,66] and to induce oxidative stress via alternative pathways including the uncoupling of NO synthase and mitochondrial dysfunction.[67] Interestingly, diesel exhaust that was filtered to remove particulate matter significantly reduced the vascular impairments observed from whole exhaust fumes, highlighting that simple interventions are available to limit the effects of air pollutants on the surrounding population.[68]

THE IMPACT OF MAJOR EVENTS IN 2020 ON AIR POLLUTION AND CVD

Naturally occurring events can lead to direct and indirect changes in air quality. Two such events in 2020 were the vast bushfires in Australia that burnt from September 2019 into January 2020, which directly increased pollution, and the COVID-19 pandemic that indirectly decreased global air pollution due to restrictions on travel and industrial processes. While most prior studies have evaluated the effects of air pollutants on CVD and mortality between different populations in the same timeframe, these events allow us to evaluate the short- and long-term effects of changes in air pollution within the same population during and after an event. This approach has the advantage of controlling for multiple variables including climate, population ethnicity, population demographics, and socio-economic factors. As such, these events allow us to directly assess the impact of perturbations in air pollution on CVD.

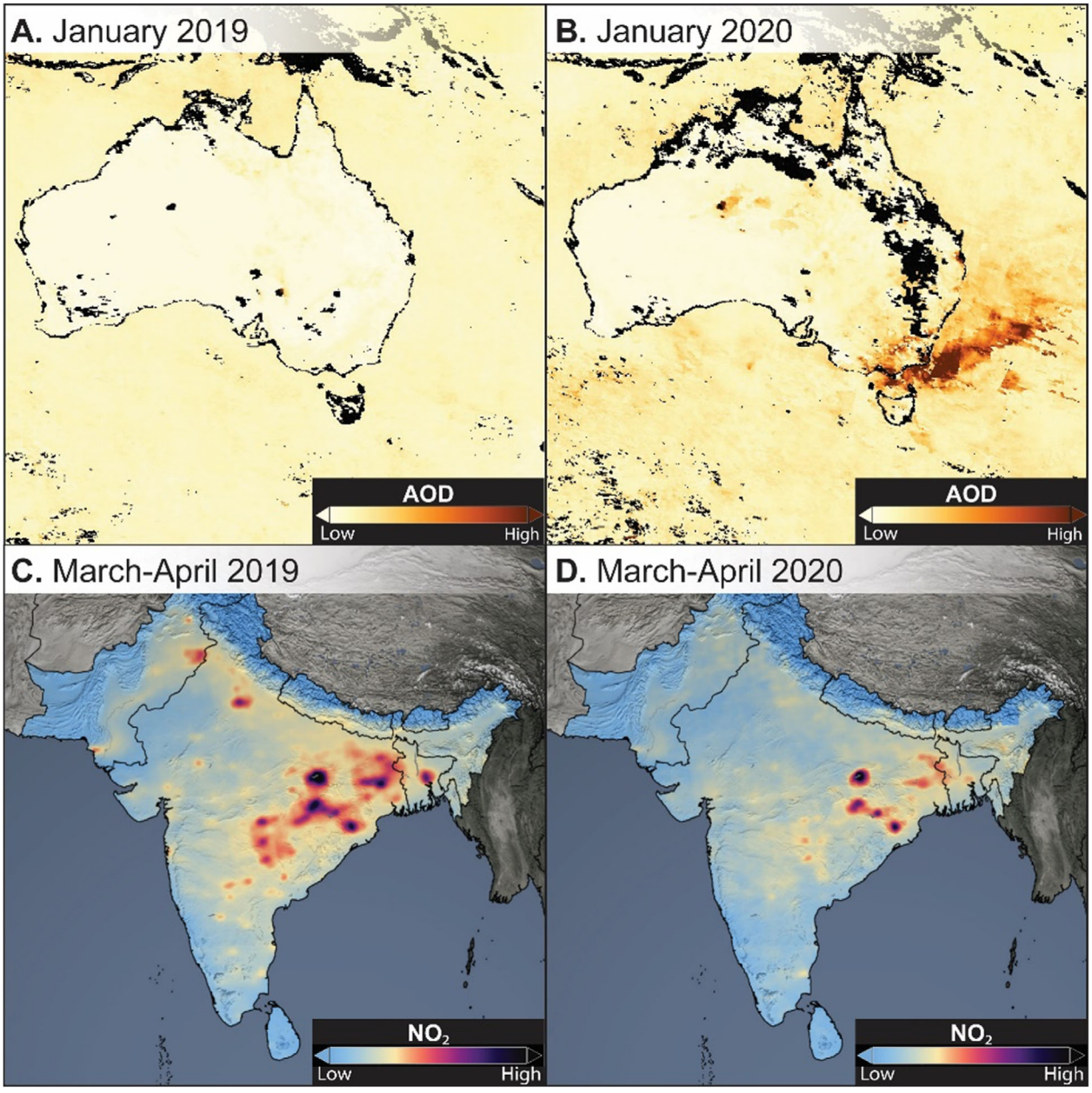

FIGURE 3 Natural events in 2020 drastically changed global levels of air pollutants. (A,B) The aerosol optical depth (AOD), detecting aerosols including smoke-derived particulate matter, across Australia was increased in January 2020 compared to January 2019 due to extensive bushfires. Image credit: NASA Earth Observations team based on data provided by the MODIS Atmosphere Science Team, NASA Goddard Space Flight Center. (C,D) The COVID-19 lockdown led to a significant decrease in NO2 emissions in major cities across the Indian subcontinent compared to the average emissions over the same period in the previous 3 years. Image credit: NASA's Scientific Visualization Studio.

Australian bushfires

The scale of the 2019–2020 Australian bushfires was unprecedented in recent history. Over 17 million hectares of land were burned across the country, according to the Australasian Fire and Emergency Service Authorities Council. At the start of January 2020, real-time air quality measurements by *IQ*Air ranked the Australian city of Canberra as having the worst air quality in the world, outranking both Delhi and Beijing. Visualizing the magnitude of the smoke released from the fires using NASA satellite imaging of the aerosol optical depth, which indicates PM levels in the atmosphere, showed a significant increase in aerosols in January 2020 compared to the same time the previous year (Figure 3A,B). The increase in observed aerosol optical depth resulting from the 2019–2020 Australian bushfire smoke broke the previous record from 2017 Canadian forest fires and the strongest volcanic eruptions of the last 29 years (Calbuco volcano in 2015 and Raikoke volcano in 2019).[69]

As a result of these fires, up to 11 million Australians were exposed to bushfire smoke with population-weighted $PM_{2.5}$ concentrations exceeding the 95th percentile of mean daily values for 125

near-consecutive days.[70] In Sydney, average $PM_{2.5}$ concentrations over 24 h exceeded 100 μg/m^3—this increase is estimated to have increased cardiovascular mortality by 4.5%.[71,72] Bushfire smoke was deemed to be responsible for an estimated 1124 excess hospitalizations for CVD and 417 excess all-cause deaths.[70] Studies on Australian bushfires in previous years have correlated smoke exposure to an elevated risk of cardiac arrest within 48 h of exposure.[73] Fire-induced elevations in PM_{10} were also associated with increased hospital admissions due to ischemic heart disease in Indigenous Australians 3 days post-exposure.[74] Data from American bushfires found that extended periods of bushfire smoke exposure of up to 1 month increased CVD mortality more than respiratory mortality, at 19% and 9%, respectively.[75]

Bushfire smoke particles tend to be small, with PM in the range of 0.4–0.7 μm, allowing for deep penetration into the lungs and impacting the cardiovascular system via several mechanisms. Smoke extract from Australian native plants was found to increase the production of pro-inflammatory mediators in cultured macrophages and impair their phagocytotic function.[76] Exposure of lung fibroblasts to smoke extract resulted in the release of cytokines that promote systemic inflammation.[77] This ability of smoke PM to induce systemic inflammation was observed in healthy volunteers who were exposed to wood smoke particles for just 2 h, which was shown to increase the number of inflammatory cells the following day.[78] Additionally, wood smoke with $PM_{2.5}$ concentrations in the range observed during the 2020 Australian bushfires has been shown to have acute effects on the cardiovascular system by significantly increasing systolic blood pressure 24 h post-exposure.[79]

Although the smoke-related health impacts from the 2020 Australian bushfires were substantial, the full extent of this will only be known after comprehensive epidemiological analyses have been performed. In terms of financial impact, it is estimated that the long-term smoke-related health burden of the 2020 bushfires will cost the Australian government approximately US$1.41 billion.[80] Importantly, it is likely that the increased frequency of major bushfires is linked to climate change and global warming.[81] Only by tackling climate change, using measures including curbing the use of fossil fuels, will we be able to address this critical global issue.

COVID-19 pandemic

In late 2019, a novel coronavirus (COVID-19) was detected in Wuhan, China, which turned into a global pandemic bringing worldwide industrial sectors and travel to a standstill. By the end of March 2020, half of the world's population was under some form of lockdown, causing drastic social and economic knock-on effects. An indirect positive effect of the COVID-19 lockdown was a drastic reduction in air pollution globally. Stringent lockdown restrictions resulted in a 90% reduction in road and air travel bringing it to a 75-year low, as assessed by the Google mobility index. Consequently, global CO_2 emissions were reduced by 8.8%, a larger decrease than any other drop-in recorded history.[82] The combined effects of the lockdown led to a reduction of 20%–30% in global NO_2 emission, a major product of fossil fuel combustion.[83] Lockdown-induced improvement of air quality was strikingly evident in India (Figure 3C,D), which saw a reduction in $PM_{2.5}$ and NO_2 of 64.7% and 65.8%, respectively.[84] Similarly, $PM_{2.5}$ was reduced in China and Europe by 30% and 17%, respectively.[85]

Because at the time of writing (February 2021) we are still in the midst of the COVID-19 pandemic, it is challenging to draw strong conclusions on how reductions in air pollution have affected CVD mortality. However, modeling studies have estimated that the short-term effect of reduced $PM_{2.5}$ levels averted 24,200 deaths in China and an additional 2,190 deaths across Europe.[85] If stringent lockdowns continue throughout 2021, this model predicts that over 300,000 deaths due to air pollution could be avoided across both regions. While this modeling only considered data from the first half of 2020, it shows the sizeable effects that reducing airborne pollutants can have on mortality.

Between January and April 2020, hospital admission from AMI decreased by 48% in Northern California, with similar decreases observed in both ST-segment elevation MI and non-ST-segment elevation MI.[86] A similar decrease was reported in Milan, however, this was predominantly in non-ST-segment elevation MI.[87] One theory is that patients with chest pain and symptoms of AMI are less likely to present at hospitals due to fear of contracting COVID-19. However, given the causal relationship between air pollution and AMI,[38] combined with the dramatic reduction in pollution over lockdown, it is conceivable that the observed decrease in AMI is directly linked to improvements in air quality.

As well as improving air quality, the "safer at home" policies employed by governments have increased time spent indoors, and when outdoors people have been encouraged to wear face masks to prevent viral transmission (Figure 4). The use of face masks has been shown to reduce inhalation of $PM_{2.5}$ and correlates with a reduced risk of cardiovascular events.[88] These measures have unintentionally mitigated exposure to ambient air pollutants and in turn, may have contributed toward the drop in pollutant-induced CVD mortality resulting from lockdown.

However, the relationship between air pollution, COVID-19 and CVD is complex with airborne pollutants proposed to exacerbate COVID-19 and CVD comorbidity (Figure 4). Patients with underlying CVD have an increased risk of mortality from COVID-19, in part due to their frailty but also because of interaction between COVID-19 and the cardiovascular system.[89,90] Despite the reduced AMI presentations during this pandemic, total CVD events have risen with data from the United Kingdom suggesting that CVD mortality has increased by 8%.[91] Potentially, this may be partly attributable to COVID-19-induced cardiovascular events, as well as people not seeking appropriate treatment when they are unwell with CVD due to fear of hospital-acquired COVID-19 infection. Additionally, a positive correlation has been found between $PM_{2.5}$ levels and COVID-19 incidence ($r = 0.67$), mortality rate ($r = 0.65$) and the case fatality rate ($r = 0.7$).[92] PM was determined to be a contributing factor in 15% of global mortality from COVID-19, which appears partially attributable to air pollutants exacerbating underlying cardiovascular conditions.[93]

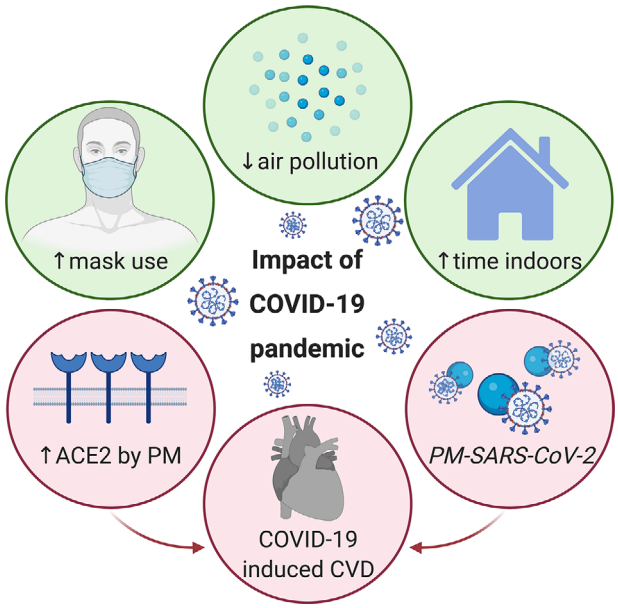

FIGURE 4 Effects of the COVID-19 pandemic on pollution-induced cardiovascular disease. The COVID-19 pandemic has had potentially positive effects by reducing exposure to air pollutants thus decreasing the risk of pollution-mediated cardiac events (green circles). These include a lockdown-induced reduction in air pollution and reduction in the inhalation of air pollutants due to increased time indoors and use of face masks while outdoors. However, the positive effects of the reduction in air pollution seen during the pandemic may be masked by confounding factors due to the interplay between pollution, COVID-19, and the cardiovascular system (red circles). Particulate matter (PM) can indue expression of ACE2, the "gateway" (receptor) for *SARS-CoV-2* into cardiac cells, and PM may form *PM-SARS-CoV-2* complexes facilitating the entry of the virus into the lungs. Together these and other factors may explain the high rates of COVID-19 and cardiovascular comorbidity

Newly emerging research has proposed that air pollution potentiates COVID-19-induced CVD by several mechanisms. Chronic exposure to $PM_{2.5}$ increases the expression of angiotensin-converting enzyme 2 (ACE2), which is present as a transmembrane protein in the cell wall of differing cardiovascular cell types (including cardiomyocytes, endothelial cells, and pericytes) as well as in the lungs, kidney, and intestines.[94,95] ACE2 normally lowers blood pressure by catalyzing the hydrolysis of angiotensin II (a vasoconstrictor peptide) into angiotensin 1–7 (a vasodilator). The *SARS-CoV-2* virus, which causes COVID-19, enters cells using ACE2 as a "gateway" to cell infection.[96] Massive viral binding to ACE2 results in a reduction in the availability of ACE2 to bind its usual substrate angiotensin II. This is speculated to lead to an increase of angiotensin-II and decreased production of the vasodilator angiotensin 1–7. Furthermore, it has been postulated that pollution-induced overexpression of ACE2 facilitates higher levels of virus binding, which increases viral load within cells and simultaneously depletes ACE2, leading to an exaggerated disease response.[92] Recent reports also suggest that *SARS-CoV-2* can absorb onto the surface of PM creating *PM-SARS-CoV-2* particles.[97] The creation of particle-virus hybrids may conceivably facilitate entry of the virus deep into the alveoli or facilitate translocation directly into the circulatory system, thus increasing viral load. As both PM and *SARS-CoV-2* are known to induce systemic inflammatory responses, their combined effects may elicit the so-called "cytokine storm" characteristic of COVID-19. In support of this theory, recent reports have found that high viral load can induce fulminant myocarditis with infiltration of inflammatory cells.[98] PM exposure is therefore proposed to mediate the adverse cardiovascular outcomes of COVID-19 by directly exerting deleterious effects and indirectly by facilitating virus entry and increasing viral load.

Taking all the above data as a whole, a complex balance of competing factors appears to be at play, juxtaposing beneficial cardiovascular effects of reduced pollution and airborne PM through the current pandemic, versus adverse cardiovascular effects of COVID-19, and additional *in vivo* and *ex vivo* interactions between COVID-19 and airborne pollutants. Epidemiological studies to determine the precise relationship between air pollution, COVID-19, and CVD are currently ongoing, but it may be some time before we fully understand the effects of these factors. However, PM-mediated COVID-19 and CVD comorbidity could mask any positive effects. The true benefits of the lockdown-induced reduction in air pollution on CVD will not become clear until detailed epidemiological studies have been undertaken. Worryingly, it is possible that the reduction in air pollution observed during the pandemic lockdown was not severe or long-lived enough to have any substantial effects on CVD mortality. Indeed even with the stringent lockdown and 30% reduction in $PM_{2.5}$, the concentration of $PM_{2.5}$ in 95 locked-down cities across China was still four times higher than deemed safe by WHO.[99]

CAN WE LEARN FROM 2020 AND CHANGE OUR WAYS?

The Australian bushfires of 2020 highlighted that increases in air pollution come with a substantial human and financial cost. Taken together with the wealth of prior data (as outlined above), it is clear that from a cardiovascular and many other perspectives, reducing ambient air pollution should be a priority. The 2020 European Environmental Plan put the reduction of emissions at the top of its agenda; however, the COVID-19 pandemic has put a substantial and prolonged strain on global industry, threatening to push the world into an economic recession. The threat of recession may lead societies to do "whatever it takes" to stimulate economic growth, thereby pushing air pollution out of the limelight. However, delays in tackling air pollution will result in major long-term health consequences, from which governments will face considerable financial repercussions.

While the stringent measures taken during the COVID-19 pandemic are not feasible or practical to continue permanently, the lockdown demonstrated that changes in human behavior can rapidly reduce air pollution. There are simpler long-term alternatives that can be employed to reduce industrial and traffic pollution than total lockdown. Measures put in place during the 2008 Beijing Olympics regulating power plant operation times and reducing traffic resulted in a 30% drop in PM_{10} concentrations across targeted cities,[100] which

was associated with a decrease in cardiovascular mortality, particularly in women and the elderly.[101] As another measure, the enforced use of higher quality gasoline in motor vehicles in China resulted in a 13% reduction in pollution across all pollutants.[102] However, moving away from our reliance on fossil fuels should be the goal. Globally fossil fuel combustion accounts for 50%–60% of human-made airborne pollutants, with up to 80% of this generated by West Asia, North America, and Europe.[93] It is estimated that by ceasing the burning of fossil fuels we could increase the global mean life expectancy by 1.1 years.[2]

In the past, government legislation has created changes that have directly reduced pollution and in turn, reduced CVD mortality. In Scotland, the 2006 ban of smoking in public places resulted in a 17% reduction in rates of hospital admission from acute coronary syndrome.[103] Interestingly non-smokers accounted for 67% of the reduction, demonstrating that second-hand smoke is a major player in the onset of acute coronary syndrome. While cigarette smoke is not directly comparable to environmental pollution, the positive effects of the smoking ban on CVD may draw parallels to the effects of reducing air pollutants.

In addition to utilizing legislature to reduce air pollution, personal measures can be taken to reduce exposure. The COVID-19 pandemic has normalized everyday wearing of face masks to prevent virus transmission. As discussed, a secondary benefit from this is a marked reduction in the inhalation of PM,[104] and it has been shown that wearing a face mask attenuates the reduction in HRV in response to PM, with N-95 masks providing the greatest level of protection.[105] These studies demonstrate the need for health care providers to integrate air pollution management into treatment plans for CVD, which could include steps such as monitoring $PM_{2.5}$ levels and wearing face masks when appropriate to reduce the risk of acute cardiovascular events.

CONCLUDING REMARKS

Reducing air pollution is perhaps one of the single most important actions we can take to actively prevent adverse health events and reduce global mortality from CVD. If we act now, we may be able to reverse some of the negative effects air pollution has had on the current generation, as recent research has demonstrated that the detrimental epigenetic changes associated with $PM_{2.5}$ exposure are reversible.[59] While we will only know the full impact of the events of 2020 on CVD with hindsight, perhaps one positive outcome from this *annus horribilis* will be the realization that we can control air pollution levels and that stringent measures could save hundreds of thousands of lives.

ACKNOWLEDGMENTS

Jason C. Kovacic acknowledges research support from the National Institutes of Health (R01HL130423, R01HL135093, and R01HL148167-01A1) and New South Wales health grant RG194194. The graphical abstract and Figures 1, 2, and 4 were created using BioRender.com.

CONFLICT OF INTEREST

There are no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Kathryn Wolhuter https://orcid.org/0000-0001-6293-9820
Manish Arora https://orcid.org/0000-0002-3350-4657

REFERENCES

1. Cohen, A. J., Brauer, M., Burnett, R., Anderson, H. R., Frostad, J., Estep, K., Balakrishnan, K., Brunekreef, B., Dandona, L., Dandona, R., Feigin, V., Freedman, G., Hubbell, B., Jobling, A., Kan, H., Knibbs, L., Liu, Y., Martin, R., Morawska, L., … Forouzanfar, M. H. (2017). Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: An analysis of data from the Global Burden of Diseases Study 2015. *Lancet*, *389*, 1907–1918.
2. Lelieveld, J., Pozzer, A., Pöschl, U., Fnais, M., Haines, A., & Münzel, T. (2020). Loss of life expectancy from air pollution compared to other risk factors: A worldwide perspective. *Cardiovascular Research*, *116*, 1910–1917.
3. Burnett, R., Chen, H., Szyszkowicz, M., Fann, N., Hubbell, B., Pope, C. A., Apte, J. S., Brauer, M., Cohen, A., Weichenthal, S., Coggins, J., Di, Q., Brunekreef, B., Frostad, J., Lim, S. S., Kan, H., Walker, K. D., Thurston, G. D., Hayes, R. B., … Spadaro, J. V. (2018). Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proceedings of the National Academy of Sciences of the United States of America*, *115*, 9592–9597.
4. Wan, G., Rajagopalan, S., Sun, Q., & Zhang, K. (2010). Real-world exposure of airborne particulate matter triggers oxidative stress in an animal model. *International Journal of Physiology, Pathophysiology and Pharmacology*, *2*, 64–68.
5. Beelen, R., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z. J., Weinmayr, G., Hoffmann, B., Wolf, K., Samoli, E., Fischer, P., Nieuwenhuijsen, M., Vineis, P., Xun, W. W., Katsouyanni, K., Dimakopoulou, K., Oudin, A., Forsberg, B., Modig, L., Havulinna, A. S., Lanki, T., … Hoek, G. (2014). Effects of long-term exposure to air pollution on natural-cause mortality: An analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet*, *383*, 785–795.
6. Song, X., Liu, Y., Hu, Y., Zhao, X., Tian, J., Ding, G., & Wang, S. (2016). Short-term exposure to air pollution and cardiac arrhythmia: A meta-analysis and systematic review. *International Journal of Environmental Research and Public Health*, *13*, 642.
7. Peters, A., Liu, E., Verrier, R. L., Schwartz, J., Gold, D. R., Mittleman, M., Baliff, J., Oh, J. A., Allen, G., Monahan, K., & Dockery, D. W. (2000). Air pollution and incidence of cardiac arrhythmia. *Epidemiology*, *11*, 11–17.
8. Oikonomou, E., Mystakidi, V.-C., Theofilis, P., Fountoulakis, P., Asimakopoulou, M., Barbaresos, N., Giannarakis, I., Vogiatzi, G., Papakonstantinou, M., Tsalamandris, S., Lazaros, G., & Tousoulis, D. (2020). The impact of air pollution on atherosclerosis burden in patients with coronary artery disease. *Journal of the American College of Cardiology*, *75*, 3463-3463.
9. Rosenlund, M., Bellander, T., Nordquist, T., & Alfredsson, L. (2009). Traffic-generated air pollution and myocardial infarction. *Epidemiology*, *20*, 265–271.
10. Shah, A. S., Langrish, J. P., Nair, H., Mcallister, D. A., Hunter, A. L., Donaldson, K., Newby, D. E., & Mills, N. L. (2013). Global association of air pollution and heart failure: A systematic review and meta-analysis. *Lancet*, *382*, 1039–1048.

11. Lakey, P. S. J., Berkemeier, T., Tong, H., Arangio, A. M., Lucas, K., Pöschl, U., & Shiraiwa, M. (2016). Chemical exposure-response relationship between air pollutants and reactive oxygen species in the human respiratory tract. *Scientific Reports*, *6*, 32916.
12. Brook, R. D., Rajagopalan, S., Pope, C. A., Brook, J. R., Bhatnagar, A., Diez-Roux, A. V., Holguin, F., Hong, Y., Luepker, R. V., Mittleman, M. A., Peters, A., Siscovick, D., Smith, S. C., Whitsel, L., Kaufman, J. D., American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, & Council on Nutrition, Physical Activity and Metabolism. (2010). Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation*, *121*, 2331–2378.
13. Steenhof, M., Gosens, I., Strak, M., Godri, K. J., Hoek, G., Cassee, F. R., Mudway, I. S., Kelly, F. J., Harrison, R. M., Lebret, E., Brunekreef, B., Janssen, N. A., & Pieters, R. H. (2011). In vitro toxicity of particulate matter (PM) collected at different sites in the Netherlands is associated with PM composition, size fraction and oxidative potential–The RAPTES project. *Particle and Fibre Toxicology*, *8*, 26.
14. Samet, J. M., Dominici, F., Curriero, F. C., Coursac, I., & Zeger, S. L. (2000). Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. *New England Journal of Medicine*, *343*, 1742–1749.
15. Pope C. A., 3rd, & Dockery, D. W. (2006). Health effects of fine particulate air pollution: Lines that connect. *Journal of the Air & Waste Management Association (1995)*, *56*, 709–742.
16. Ostro, B., Broadwin, R., Green, S., Feng, W.-Y., & Lipsett, M. (2006). Fine particulate air pollution and mortality in nine California counties: Results from CALFINE. *Environmental Health Perspectives*, *114*, 29–33.
17. Klemm, R. J., Mason R. M., Jr., Heilig, C. M., Neas, L. M., & Dockery, D. W. (2000). Is daily mortality associated specifically with fine particles? Data reconstruction and replication of analyses. *Journal of the Air & Waste Management Association (1995)*, *50*, 1215–1222.
18. Daigle, C. C., Chalupa, D. C., Gibb, F. R., Morrow, P. E., Oberdörster, G., Utell, M. J., & Frampton, M. W. (2003). Ultrafine particle deposition in humans during rest and exercise. *Inhalation Toxicology*, *15*, 539–552.
19. Nemmar, A., Vanbilloen, H., Hoylaerts, M. F., Hoet, P. H. M., Verbruggen, A., & Nemery, B. (2001). Passage of intratracheally instilled ultrafine particles from the lung into the systemic circulation in hamster. *American Journal of Respiratory and Critical Care Medicine*, *164*, 1665–1668.
20. Nemmar, A., Hoet, P. H. M., Vanquickenborne, B., Dinsdale, D., Thomeer, M., Hoylaerts, M. F., Vanbilloen, H., Mortelmans, L., & Nemery, B. (2002). Passage of inhaled particles into the blood circulation in humans. *Circulation*, *105*, 411–414.
21. Bauer, M., Moebus, S., Möhlenkamp, S., Dragano, N., Nonnemacher, M., Fuchsluger, M., Kessler, C., Jakobs, H., Memmesheimer, M., Erbel, R., Jöckel, K.-H., Hoffmann, B., & HNR Study Investigative Group. (2010). Urban particulate matter air pollution is associated with subclinical atherosclerosis: Results from the HNR (Heinz Nixdorf Recall) study. *Journal of the American College of Cardiology*, *56*, 1803–1808.
22. Tang, L., Wang, Q.-Y., Cheng, Z.-P., Hu, B., Liu, J.-D., & Hu, Y. (2016). Air pollution and venous thrombosis: A meta-analysis. *Scientific Reports*, *6*, 32794.
23. Shah, A. S. V., Lee, K. K., McAllister, D. A., Hunter, A., Nair, H., Whiteley, W., & Mills, N. L. (2015). Short term exposure to air pollution and stroke: Systematic review and meta-analysis. *BMJ (Clinical Research Ed.)*, *350*, h1295.
24. Folino, F., Buja, G., Zanotto, G., Marras, E., Allocca, G., Vaccari, D., Gasparini, G., Bertaglia, E., Zoppo, F., Calzolari, V., Suh, R. N., Ignatiuk, B., Lanera, C., Benassi, A., Gregori, D., & Iliceto, S. (2017). Association between air pollution and ventricular arrhythmias in high-risk patients (ARIA study): A multicentre longitudinal study. *Lancet Planetary Health*, *1*, e58-e64.
25. Zhao, B., Johnston, F. H., Salimi, F., Kurabayashi, M., & Negishi, K. (2020). Short-term exposure to ambient fine particulate matter and out-of-hospital cardiac arrest: A nationwide case-crossover study in Japan. *Lancet Planetary Health*, *4*, e15-e23.
26. Miller, M. R., & Newby, D. E. (2020). Air pollution and cardiovascular disease: Car sick. *Cardiovascular Research*, *116*, 279–294.
27. Rajagopalan, S., Al-Kindi, S. G., & Brook, R. D. (2018). Air pollution and cardiovascular disease: JACC state-of-the-art review. *Journal of the American College of Cardiology*, *72*, 2054–2070.
28. Niemann, B., Rohrbach, S., Miller, M. R., Newby, D. E., Fuster, V., & Kovacic, J. C. (2017). Oxidative stress and cardiovascular risk: Obesity, diabetes, smoking, and pollution: Part 3 of a 3-part series. *Journal of the American College of Cardiology*, *70*, 230–251.
29. Brook, R. D., & Rajagopalan, S. (2009). Particulate matter, air pollution, and blood pressure. *Journal of the American Society of Hypertension*, *3*, 332–350.
30. Liang, R., Zhang, B., Zhao, X., Ruan, Y., Lian, H., & Fan, Z. (2014). Effect of exposure to PM2.5 on blood pressure: A systematic review and meta-analysis. *Journal of Hypertension*, *32*, 2130-2141; discussion 2141.
31. Sun, Q. (2005). Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. *JAMA*, *294*, 3003–3010.
32. Yang, S., Lee, S.-P., Park, J.-B., Lee, H., Kang, S.-H., Lee, S.-E., Kim, J. B., Choi, S.-Y., Kim, Y.-J., & Chang, H.-J. (2019). PM2.5 concentration in the ambient air is a risk factor for the development of high-risk coronary plaques. *European Heart Journal - Cardiovascular Imaging*, *20*, 1355–1364.
33. Estol, C. J. (2019). Is breathing our polluted air a risk factor for stroke? *International Journal of Stroke*, *14*, 340–350.
34. Huang, K., Liang, F., Yang, X., Liu, F., Li, J., Xiao, Q., Chen, J., Liu, X., Cao, J., Shen, C., Yu, L., Lu, F., Wu, X., Zhao, L., Wu, X., Li, Y., Hu, D., Huang, J., Liu, Y., … Gu, D. (2019). Long term exposure to ambient fine particulate matter and incidence of stroke: Prospective cohort study from the China-PAR project. *BMJ (Clinical Research Ed.)*, *367*, l6720.
35. Hong, Y.-C., Lee, J.-T., Kim, H., & Kwon, H.-J. (2002). Air pollution: A new risk factor in ischemic stroke mortality. *Stroke; A Journal of Cerebral Circulation*, *33*, 2165–2169.
36. Oudin, A., Forsberg, B., & Jakobsson, K. (2012). Air pollution and stroke. *Epidemiology*, *23*, 505–506.
37. Dai H.Much A. A.Maor E.Asher E.Younis A.Xu Y.Lu Y.Liu X.Shu J., & Bragazzi N. L. (2020). Global, regional, and national burden of ischemic heart disease and its attributable risk factors, 1990–2017: Results from the global Burden of Disease Study 2017. *European Heart Journal – Quality of Care and Clinical Outcomes*. https://doi.org/10.1093/ehjqcco/qcaa076
38. Bai, L., Shin, S., Burnett, R. T., Kwong, J. C., Hystad, P., Van Donkelaar, A., Goldberg, M. S., Lavigne, E., Copes, R., Martin, R. V., Kopp, A., & Chen, H. (2019). Exposure to ambient air pollution and the incidence of congestive heart failure and acute myocardial infarction: A population-based study of 5.1 million Canadian adults living in Ontario. *Environment International*, *132*, 105004.
39. Bhaskaran, K., Hajat, S., Armstrong, B., Haines, A., Herrett, E., Wilkinson, P., & Smeeth, L. (2011). The effects of hourly differences in air pollution on the risk of myocardial infarction: Case crossover analysis of the MINAP database. *BMJ (Clinical Research Ed.)*, *343*, d5531.
40. Peters, A., Von Klot, S., Mittleman, M. A., Meisinger, C., Hörmann, A., Kuch, B., & Wichmann, H. E. (2013). Triggering of acute myocardial infarction by different means of transportation. *European Journal of Preventive Cardiology*, *20*, 750–758.
41. Buteau, S., & Goldberg, M. S. (2016). A structured review of panel studies used to investigate associations between ambient air pollution and heart rate variability. *Environmental Research*, *148*, 207–247.

42. Devlin, R. B., Ghio, A. J., Kehrl, H., Sanders, G., & Cascio, W. (2003). Elderly humans exposed to concentrated air pollution particles have decreased heart rate variability. *European Respiratory Journal*, *21*, 76s-80s.
43. Carll, A. P., Haykal-Coates, N., Winsett, D. W., Hazari, M. S., Ledbetter, A. D., Richards, J. H., Cascio, W. E., Costa, D. L., & Farraj, A. K. (2015). Cardiomyopathy confers susceptibility to particulate matter-induced oxidative stress, vagal dominance, arrhythmia and pulmonary inflammation in heart failure-prone rats. *Inhalation Toxicology*, *27*, 100–112.
44. Carll, A. P., Lust, R. M., Hazari, M. S., Perez, C. M., Krantz, Q. T., King, C. J., Winsett, D. W., Cascio, W. E., Costa, D. L., & Farraj, A. K. (2013). Diesel exhaust inhalation increases cardiac output, bradyarrhythmias, and parasympathetic tone in aged heart failure-prone rats. *Toxicological Sciences*, *131*, 583–595.
45. Carll, A. P., Haykal-Coates, N., Winsett, D. W., Rowan, W. H., Hazari, M. S., Ledbetter, A. D., Nyska, A., Cascio, W. E., Watkinson, W. P., Costa, D. L., & Farraj, A. K. (2010). Particulate matter inhalation exacerbates cardiopulmonary injury in a rat model of isoproterenol-induced cardiomyopathy. *Inhalation Toxicology*, *22*, 355–368.
46. Kodavanti, U. P. (2016). Stretching the stress boundary: Linking air pollution health effects to a neurohormonal stress response. *Biochimica Et Biophysica Acta*, *1860*, 2880–2890.
47. Pope, C. A., Verrier, R. L., Lovett, E. G., Larson, A. C., Raizenne, M. E., Kanner, R. E., Schwartz, J., Villegas, G. M., Gold, D. R., & Dockery, D. W. (1999). Heart rate variability associated with particulate air pollution. *American Heart Journal*, *138*, 890–899.
48. Robertson, S., Thomson, A. L., Carter, R., Stott, H. R., Shaw, C. A., Hadoke, P. W. F., Newby, D. E., Miller, M. R., & Gray, G. A. (2014). Pulmonary diesel particulate increases susceptibility to myocardial ischemia/reperfusion injury via activation of sensory TRPV1 and beta1 adrenoreceptors. *Particle and Fibre Toxicology*, *11*, 12.
49. Robinson, R. K., Birrell, M. A., Adcock, J. J., Wortley, M. A., Dubuis, E. D., Chen, S., Mcgilvery, C. M., Hu, S., Shaffer, M. S. P., Bonvini, S. J., Maher, S. A., Mudway, I. S., Porter, A. E., Carlsten, C., Tetley, T. D., & Belvisi, M. G. (2018). Mechanistic link between diesel exhaust particles and respiratory reflexes. *Journal of Allergy and Clinical Immunology*, *141*, 1074–1084.e9.
50. Calderon-Garciduenas, L., Gonzalez-Maciel, A., Reynoso-Robles, R., Delgado-Chavez, R., Mukherjee, P. S., Kulesza, R. J., Torres-Jardón, R., Ávila-Ramírez, J., & Villarreal-Rios, R. (2018). Hallmarks of Alzheimer disease are evolving relentlessly in Metropolitan Mexico City infants, children and young adults. APOE4 carriers have higher suicide risk and higher odds of reaching NFT stage V at ≤ 40 years of age. *Environmental Research*, *164*, 475–487.
51. Maher, B. A., Ahmed, I. A. M., Karloukovski, V., Maclaren, D. A., Foulds, P. G., Allsop, D., Mann, D. M. A., Torres-Jardón, R., & Calderon-Garciduenas, L. (2016). Magnetite pollution nanoparticles in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *113*, 10797–10801.
52. Miller, M. R., Raftis, J. B., Langrish, J. P., Mclean, S. G., Samutrtai, P., Connell, S. P., Wilson, S., Vesey, A. T., Fokkens, P. H. B., Boere, A. J. F., Krystek, P., Campbell, C. J., Hadoke, P. W. F., Donaldson, K., Cassee, F. R., Newby, D. E., Duffin, R., & Mills, N. L. (2017). Inhaled nanoparticles accumulate at sites of vascular disease. *ACS Nano*, *11*, 4542–4552.
53. Shaw, C. A., Mortimer, G. M., Deng, Z. J., Carter, E. S., Connell, S. P., Miller, M. R., Duffin, R., Newby, D. E., Hadoke, P. W. F., & Minchin, R. F. (2016). Protein corona formation in bronchoalveolar fluid enhances diesel exhaust nanoparticle uptake and pro-inflammatory responses in macrophages. *Nanotoxicology*, *10*, 981–991.
54. Shaw, C. A., Robertson, S., Miller, M. R., Duffin, R., Tabor, C. M., Donaldson, K., Newby, D. E., & Hadoke, P. W. F. (2011). Diesel exhaust particulate–exposed macrophages cause marked endothelial cell activation. *American Journal of Respiratory Cell and Molecular Biology*, *44*, 840–851.
55. Goodman, J. E., Prueitt, R. L., Sax, S. N., Pizzurro, D. M., Lynch, H. N., Zu, K., & Venditti, F. J. (2015). Ozone exposure and systemic biomarkers: Evaluation of evidence for adverse cardiovascular health impacts. *Critical Reviews in Toxicology*, *45*, 412–452.
56. Robertson, S., Gray, G. A., Duffin, R., Mclean, S. G., Shaw, C. A., Hadoke, P. W., Newby, D. E., & Miller, M. R. (2012). Diesel exhaust particulate induces pulmonary and systemic inflammation in rats without impairing endothelial function ex vivo or in vivo. *Particle and Fibre Toxicology*, *9*, 9.
57. Forbes, L. J. L., Patel, M. D., Rudnicka, A. R., Cook, D. G., Bush, T., Stedman, J. R., Whincup, P. H., Strachan, D. P., & Anderson, R. H. (2009). Chronic exposure to outdoor air pollution and markers of systemic inflammation. *Epidemiology*, *20*, 245–253.
58. Miller, M. R., Shaw, C. A., & Langrish, J. P. (2012). From particles to patients: Oxidative stress and the cardiovascular effects of air pollution. *Future Cardiology*, *8*, 577–602.
59. Rajagopalan, S., Park, B., Palanivel, R., Vinayachandran, V., Deiuliis, J. A., Gangwar, R. S., Das, L., Yin, J., Choi, Y., Al-Kindi, S., Jain, M. K., Hansen, K. D., & Biswal, S. (2020). Metabolic effects of air pollution exposure and reversibility. *Journal of Clinical Investigation*, *130*, 6034–6040.
60. Chen, R., Meng, X., Zhao, A., Wang, C., Yang, C., Li, H., Cai, J., Zhao, Z., & Kan, H. (2016). DNA hypomethylation and its mediation in the effects of fine particulate air pollution on cardiovascular biomarkers: A randomized crossover trial. *Environment International*, *94*, 614–619.
61. Li, H., Chen, R., Cai, J., Cui, X., Huang, N., & Kan, H. (2018). Short-term exposure to fine particulate air pollution and genome-wide DNA methylation: A randomized, double-blind, crossover trial. *Environment International*, *120*, 130–136.
62. Mills, N. L., TöRnqvist, H., Robinson, S. D., Gonzalez, M., Darnley, K., Macnee, W., Boon, N. A., Donaldson, K., Blomberg, A., Sandstrom, T., & Newby, D. E. (2005). Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. *Circulation*, *112*, 3930–3936.
63. Törnqvist, H., Mills, N. L., Gonzalez, M., Miller, M. R., Robinson, S. D., Megson, I. L., Macnee, W., Donaldson, K., Söderberg, S., Newby, D. E., Sandström, T., & Blomberg, A. (2007). Persistent endothelial dysfunction in humans after diesel exhaust inhalation. *American Journal of Respiratory and Critical Care Medicine*, *176*, 395–400.
64. Lucking, A. J., Lundback, M., Mills, N. L., Faratian, D., Barath, S. L., Pourazar, J., Cassee, F. R., Donaldson, K., Boon, N. A., Badimon, J. J., Sandstrom, T., Blomberg, A., & Newby, D. E. (2008). Diesel exhaust inhalation increases thrombus formation in man. *European Heart Journal*, *29*, 3043–3051.
65. Miller, M. R., Borthwick, S. J., Shaw, C. A., Mclean, S. G., Mcclure, D., Mills, N. L., Duffin, R., Donaldson, K., Megson, I. L., Hadoke, P. W. F., & Newby, D. E. (2009). Direct impairment of vascular function by diesel exhaust particulate through reduced bioavailability of endothelium-derived nitric oxide induced by superoxide free radicals. *Environmental Health Perspectives*, *117*, 611–616.
66. Donaldson, K., Brown, D. M., Mitchell, C., Dineva, M., Beswick, P. H., Gilmour, P., & Macnee, W. (1997). Free radical activity of PM10: Iron-mediated generation of hydroxyl radicals. *Environmental Health Perspectives*, *105*(Suppl 5), 1285–1289.
67. Risom, L., Møller, P., & Loft, S. (2005). Oxidative stress-induced DNA damage by particulate air pollution. *Mutation Research*, *592*, 119–137.
68. Mills, N. L., Miller, M. R., Lucking, A. J., Beveridge, J., Flint, L., Boere, A. J. F., Fokkens, P. H., Boon, N. A., Sandstrom, T., Blomberg, A., Duffin, R., Donaldson, K., Hadoke, P. W. F., Cassee, F. R., & Newby, D. E. (2011). Combustion-derived nanoparticulate induces the adverse vascular effects of diesel exhaust inhalation. *European Heart Journal*, *32*, 2660–2671.

69. Khaykin, S., Legras, B., Bucci, S., Sellitto, P., Isaksen, L., Tencé, F., Bekki, S., Bourassa, A., Rieger, L., Zawada, D., Jumelet, J., & Godin-Beekmann, S. (2020). The 2019/20 Australian wildfires generated a persistent smoke-charged vortex rising up to 35 km altitude. *Communications Earth & Environment*, *1*, 22.
70. Borchers Arriagada, N., Palmer, A. J., Bowman, D. M., Morgan, G. G., Jalaludin, B. B., & Johnston, F. H. (2020). Unprecedented smoke-related health burden associated with the 2019–20 bushfires in eastern Australia. *Medical Journal of Australia*, *213*, 282–283.
71. Yu, P., Xu, R., Abramson, M. J., Li, S., & Guo, Y. (2020). Bushfires in Australia: A serious health emergency under climate change. *Lancet Planetary Health*, *4*, e7-e8.
72. Liu, C., Chen, R., Sera, F., Vicedo-Cabrera, A. M., Guo, Y., Tong, S., Coelho, M. S. Z. S., Saldiva, P. H. N., Lavigne, E., Matus, P., Valdes Ortega, N., Osorio Garcia, S., Pascal, M., Stafoggia, M., Scortichini, M., Hashizume, M., Honda, Y., Hurtado-Díaz, M., Cruz, J., … Kan, H. (2019). Ambient particulate air pollution and daily mortality in 652 cities. *New England Journal of Medicine*, *381*, 705–715.
73. Haikerwal, A., Akram, M., Del Monaco, A., Smith, K., Sim, M. R., Meyer, M., Tonkin, A. M., Abramson, M. J., & Dennekamp, M. (2015). Impact of fine particulate matter (PM2.5) exposure during wildfires on cardiovascular health outcomes. *Journal of the American Heart Association*, *4*, e001653.
74. Hanigan, I. C., Johnston, F. H., & Morgan, G. G. (2008). Vegetation fire smoke, indigenous status and cardio-respiratory hospital admissions in Darwin, Australia, 1996–2005: A time-series study. *Environmental Health*, *7*, 42.
75. Liu, Y., Austin, E., Xiang, J., Gould, T., Larson, T., & Seto, E. (2020). Health impact assessment of PM 2.5 attributable mortality from the September 2020 Washington State wildfire smoke episode. *medRxiv*. https://doi.org/10.1101/2020.09.19.20197921
76. Hamon, R., Tran, H. B., Roscioli, E., Ween, M., Jersmann, H., & Hodge, S. (2018). Bushfire smoke is pro-inflammatory and suppresses macrophage phagocytic function. *Scientific Reports*, *8*, 13424.
77. Krimmer, D., Ichimaru, Y., Burgess, J., Black, J., & Oliver, B. (2013). Exposure to biomass smoke extract enhances fibronectin release from fibroblasts. *PLoS One*, *8*, e83938.
78. Ghio, A. J., Soukup, J. M., Case, M., Dailey, L. A., Richards, J., Berntsen, J., Devlin, R. B., Stone, S., & Rappold, A. (2012). Exposure to wood smoke particles produces inflammation in healthy volunteers. *Occupational and Environmental Medicine*, *69*, 170–175.
79. Fedak, K. M., Good, N., Walker, E. S., Balmes, J., Brook, R. D., Clark, M. L., Cole-Hunter, T., Devlin, R., L'orange, C., Luckasen, G., Mehaffy, J., Shelton, R., Wilson, A., Volckens, J., & Peel, J. L. (2019). Acute effects on blood pressure following controlled exposure to cookstove air pollution in the STOVES study. *Journal of the American Heart Association*, *8*, e012246.
80. Johnston, F. H., Borchers-Arriagada, N., Morgan, G. G., Jalaludin, B., Palmer, A. J., Williamson, G. J., & Bowman, D. M. J. S. (2020). Unprecedented health costs of smoke-related PM2.5 from the 2019–20 Australian megafires. *Nature Sustainability*, *4*, 42–47.
81. Xu, R., Yu, P., Abramson, M. J., Johnston, F. H., Samet, J. M., Bell, M. L., Haines, A., Ebi, K. L., Li, S., & Guo, Y. (2020). Wildfires, global climate change, and human health. *New England Journal of Medicine*, *383*, 2173–2181.
82. Liu, Z., Ciais, P., Deng, Z., Lei, R., Davis, S. J., Feng, S., Zheng, B., Cui, D., Dou, X., Zhu, B., Guo, R., Ke, P., Sun, T., Lu, C., He, P., Wang, Y., Yue, X., Wang, Y., Lei, Y., … Schellnhuber, H. J. (2020). Near-real-time monitoring of global CO2 emissions reveals the effects of the COVID-19 pandemic. *Nature communications*, *11*, 5172.
83. Muhammad, S., Long, X., & Salman, M. (2020). COVID-19 pandemic and environmental pollution: A blessing in disguise? *The Science of the Total Environment*, *728*, 138820.
84. Agarwal, A., Kaushik, A., Kumar, S., & Mishra, R. K. (2020). Comparative study on air quality status in Indian and Chinese cities before and during the COVID-19 lockdown period. *Air Quality, Atmosphere and Health*, *13*, 1167–1178.
85. Giani, P., Castruccio, S., Anav, A., Howard, D., Hu, W., & Crippa, P. (2020). Short-term and long-term health impacts of air pollution reductions from COVID-19 lockdowns in China and Europe: A modelling study. *Lancet Planetary Health*, *4*, e474-e482.
86. Solomon, M. D., Mcnulty, E. J., Rana, J. S., Leong, T. K., Lee, C., Sung, S.-H., Ambrosy, A. P., Sidney, S., & Go, A. S. (2020). The Covid-19 pandemic and the incidence of acute myocardial infarction. *New England Journal of Medicine*, *383*, 691–693.
87. Stefanini, G. G., Azzolini, E., & Condorelli, G. (2020). Critical organizational issues for cardiologists in the COVID-19 outbreak: A frontline experience from Milan, Italy. *Circulation*, *141*, 1597–1599.
88. Langrish, J. P., Mills, N. L., Chan, J. K., Leseman, D. L., Aitken, R. J., Fokkens, P. H., Cassee, F. R., Li, J., Donaldson, K., Newby, D. E., & Jiang, L. (2009). Beneficial cardiovascular effects of reducing exposure to particulate air pollution with a simple facemask. *Particle and Fibre Toxicology*, *6*, 8.
89. Gori, T., Lelieveld, J., & Münzel, T. (2020). Perspective: cardiovascular disease and the Covid-19 pandemic. *Basic Research in Cardiology*, *115*, 32.
90. Nishiga, M., Wang, D. W., Han, Y., Lewis, D. B., & Wu, J. C. (2020). COVID-19 and cardiovascular disease: From basic mechanisms to clinical perspectives. *Nature Reviews Cardiology*, *17*, 543–558.
91. Wu, J., Mamas, M. A., Mohamed, M. O., Kwok, C. S., Roebuck, C., Humberstone, B., Denwood, T., Luescher, T., De Belder, M. A., Deanfield, J. E., & Gale, C. P. (2021). Place and causes of acute cardiovascular mortality during the COVID-19 pandemic. *Heart*, *107*, 113–119.
92. Borro, M., Di Girolamo, P., Gentile, G., De Luca, O., Preissner, R., Marcolongo, A., Ferracuti, S., & Simmaco, M. (2020). Evidence-based considerations exploring relations between SARS-CoV-2 pandemic and air pollution: Involvement of PM2.5-mediated up-regulation of the viral receptor ACE-2. *International Journal of Environmental Research and Public Health*, *17*, 5573.
93. Pozzer, A., Dominici, F., Haines, A., Witt, C., Münzel, T., & Lelieveld, J. (2020). Regional and global contributions of air pollution to risk of death from COVID-19. *Cardiovascular Research*, *116*, 2247–2253.
94. Lin, C.-I., Tsai, C.-H., Sun, Y.-L., Hsieh, W.-Y., Lin, Y.-C., Chen, C.-Y., & Lin, C.-S. (2018). Instillation of particulate matter 2.5 induced acute lung injury and attenuated the injury recovery in ACE2 knockout mice. *International Journal of Biological Sciences*, *14*, 253–265.
95. Miyashita, L., Foley, G., Semple, S., & Grigg, J. (2020). Traffic-derived particulate matter and angiotensin-converting enzyme 2 expression in human airway epithelial cells. *bioRxiv*. https://doi.org/10.1101/2020.05.15.097501
96. Chen, L., Li, X., Chen, M., Feng, Y., & Xiong, C. (2020). The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovascular Research*, *116*, 1097–1100.
97. Tanwar, V., Adelstein, J. M., & Wold, L. E. (2021). Double trouble: Combined cardiovascular effects of particulate matter exposure and coronavirus disease 2019. *Cardiovascular Research*, *117*, 85–95.
98. Liu, K., Fang, Y.-Y., Deng, Y., Liu, W., Wang, M.-F., Ma, J.-P., Xiao, W., Wang, Y.-N., Zhong, M.-H., Li, C.-H., Li, G.-C., & Liu, H.-G. (2020). Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chinese Medical Journal*, *133*, 1025–1031.
99. He, G., Pan, Y., & Tanaka, T. (2020). The short-term impacts of COVID-19 lockdown on urban air pollution in China. *Nature Sustainability*, *3*, 1005-1011.
100. Chen, Y., Jin, G. Z., Kumar, N., & Shi, G. (2013). The promise of Beijing: Evaluating the impact of the 2008 Olympic Games on air quality. *Journal of Environmental Economics and Management*, *66*, 424–443.
101. Su, C., Hampel, R., Franck, U., Wiedensohler, A., Cyrys, J., Pan, X., Wichmann, H.-E., Peters, A., Schneider, A., & Breitner, S. (2015). Assessing responses of cardiovascular mortality to particulate

matter air pollution for pre-, during- and post-2008 Olympics periods. *Environmental Research*, *142*, 112–122.
102. Li, P., Lu, Y., & Wang, J. (2020). The effects of fuel standards on air pollution: Evidence from China. *Journal of Development Economics*, *146*, 102488.
103. Pell, J. P., Haw, S., Cobbe, S., Newby, D. E., Pell, A. C. H., Fischbacher, C., Mcconnachie, A., Pringle, S., Murdoch, D., Dunn, F., Oldroyd, K., Macintyre, P., O'rourke, B., & Borland, W. (2008). Smoke-free legislation and hospitalizations for acute coronary syndrome. *New England Journal of Medicine*, *359*, 482–491.
104. Qian, Y., Willeke, K., Grinshpun, S. A., Donnelly, J., & Coffey, C. C. (1998). Performance of N95 respirators: Filtration efficiency for airborne microbial and inert particles. *American Industrial Hygiene Association Journal*, *59*, 128–132.
105. Yang, X., Jia, X., Dong, W., Wu, S., Miller, M. R., Hu, D., Li, H., Pan, L., Deng, F., & Guo, X. (2018). Cardiovascular benefits of reducing personal exposure to traffic-related noise and particulate air pollution: A randomized crossover study in the Beijing subway system. *Indoor Air*, *28*, 777–786.

How to cite this article: Wolhuter, K., Arora, M., & Kovacic, J. C. (2021). Air pollution and cardiovascular disease: Can the Australian bushfires and global COVID-19 pandemic of 2020 convince us to change our ways? *BioEssays*, *43*, e2100046. https://doi.org/10.1002/bies.202100046