Neurochemistry International 139 (2020) 104796

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

Review

The potential impact of bushfire smoke on brain health

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ARTICLE INFO

Keywords:
Air pollution
Bushfire smoke
Bushfire PM
Brain health
Neurotoxicity

ABSTRACT

Smoke from bushfires (also known as wildfires or forest fires) has blanketed large regions of Australia during the southern hemisphere summer of 2019/2020, potentially endangering residents who breathe the polluted air. While such air pollution is known to cause respiratory irritation and damage, its effect on the brain is not well described. In this review, we aim to outline the potentially damaging effects of bushfire smoke on brain health. We also describe the composition of air pollution, including ambient particulate matter (PM) and bushfire PM, before covering the general health effects of each. The investigated entry routes for ambient PM and postulated entry routes for bushfire PM are discussed, along with epidemiological and experimental evidence of the effect of both PMs in the brain. It appears that bushfire PM may be more toxic than ambient PM, and that it may enter the brain through extrapulmonary or olfactory routes to cause inflammation and oxidative stress. Ultimately, this review highlights the desperate requirement of greater research into the effects of bushfire PM on brain health.

1. Introduction

Australia has experienced what is arguably its most destructive bushfire (wildfire or forest fire) season in history (southern hemisphere summer of 2019/2020). Fire-fighting teams, residents and the native wildlife have all been negatively impacted. Importantly, general population health is at risk, as the recent bushfires/wildfires have covered much of Eastern Australia and even New Zealand in thick smoke (Nolan et al., 2020) dramatically decreasing the air quality. In fact, the air has been reported to be, for a time, of equal quality to some of the most highly populated and polluted cities in the world (Nogrady, 2019). Unfortunately, due to the rising threat of climate change, it is expected that the bushfire season will increase in frequency and severity (Steffin, 2013). It is now more important than ever to understand the population health effects of prolonged exposure to bushfire-derived pollution.

The negative effect of air pollution, primarily ambient air pollution from vehicles or industrial coal burning, in the respiratory system has been well established and informs air quality regulations in Australia (Spickett et al., 2011). The respiratory effect of bushfire smoke has also been investigated, and bushfire smoke has been postulated to be equally, if not more damaging to respiratory cells than ambient air pollution (Franzi et al., 2011). Studies have also demonstrated that ambient air pollution can enter the brain and cause oxidative stress and inflammation, though there has been little focus on the effects of bushfire smoke in brain health. As fires are predicted to become an increasingly frequent event in Australia and worldwide due to climate change, it is important to understand the possible effects of bushfire smoke on the brain. This review summarises the general health effects, brain routes of entry and neurological effects of ambient air pollution and bushfire smoke and concludes that bushfire smoke is a potential threat to brain health.

2. Air pollution composition

Air pollution is a heterogenous mixture of gases, metals and particulate matter (PM; Fig. 1) (Vallero, 2014). PM is regarded as a biologically important component of air pollution (Moller et al., 2010; Morakinyo et al., 2016), and sources can include vehicle emissions, brake-pad dust, industry pollution, solid fuel combustion in domestic heating, or bushfire smoke. The PM level and impact can depend on altitude, location and climate events. This review will refer to ambient PM, meaning pollution found in the urban air, the majority of which is comprised of vehicle emissions and industry pollution, and bushfire PM, meaning PM sourced mostly from bushfire smoke.

The chemical components of PM differ depending on its source. Ambient PM primarily consists of sulphate, nitrate, organic carbon (OC), elemental carbon (EC), ammonium, salt, and mineral dust (Kundu and Stone, 2014; Pöschl, 2005). This heterogeneous mixture is similar to that of bushfire smoke, though bushfire PM primarily consists of organic carbon (OC), elemental carbon (EC) and polycyclic aromatic hydrocarbons (PAH). Liu and Peng (2019) showed that wildfire smoke increased

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https://doi.org/10.1016/j.neuint.2020.104796
Received 3 March 2020; Received in revised form 20 May 2020; Accepted 22 June 2020
Available online 8 July 2020

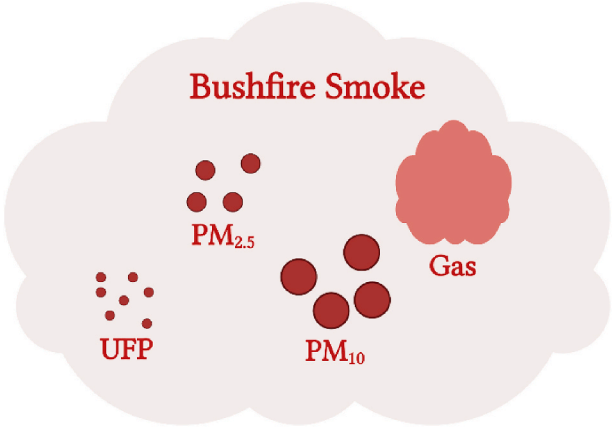

Fig. 1. Composition of Bushfire Smoke. UFP: Ultrafine particles; $PM_{2.5}$: particulate matter less than 2.5 μm in diameter; PM10: particulate matter less than 10 μm in diameter. Image created using BioRender.com.

the OC and EC components of PM as compared to ambient PM (Liu and Peng, 2019). Moreover, Zhang and Tao (2009) demonstrated that bushfire smoke is a major contributor to global PAH emissions (Zhang and Tao, 2009). Reyes et al. (2018) found a significantly higher concentration of PAH in close proximity as compared to further distances from a North Carolina, USA wildfire (Reyes et al., 2018), and Wentworth et al. (2018) reported a daily increase in PAH during a 2016 fire (Wentworth et al., 2018). The proportion of these elements and the concentration of PM depends largely on the bushfire burn efficiency. Smouldering fire, characterised by incomplete combustion, yields a higher proportion of OC (Huang et al., 2015) and PAH (Robinson et al., 2008), and a higher concentration of PM as compared to a flaming fire which is characterised by complete combustion (De Vos et al., 2009). Flaming fire does, however, yield more EC than smouldering fire (Huang et al., 2015). Bushfires have flaming and smouldering phases, with the flaming phase occurring immediately and lasting only minutes, and the smouldering phase following for hours or days. In some cases, such as the Indonesian peat fires, the smouldering phase can last for weeks (Page and Hooijer, 2016). Hence, bushfire PM will contain elements of both flaming and smouldering fire emissions, though will have a higher proportion of those seen in smouldering fire, such as a high proportion of PAH and OC and a high concentration of PM. Overall, bushfire PM differs from ambient PM in its higher proportion of EC, OC and PAH, and a high concentration of PM given a long smouldering phase.

The size of PM is another important consideration for bushfire and ambient PM alike. While PM with an aerodynamic diameter less than 10 μm (PM_{10}) is believed to cause respiratory irritation (Hoek et al., 2012), PM less than 2.5 μm in diameter ($PM_{2.5}$) has been shown to lodge deep in the lungs, enter circulation and reach other organs to cause effect (reviewed in (Schraufnagel et al., 2019)). Ultrafine particles (UFP) of less than 100 nm in diameter have also been reported and could have further damaging effects (reviewed in (Frampton and Rich, 2016)). However, due to their small size, they have been difficult to study. Overall, it is generally accepted that $PM_{2.5}$ and especially UFP are a threat to population health. Both bushfire and ambient PM consist of a heterogeneous mixture of each particle size.

3. Health effects of air pollution

3.1. Ambient PM

It has been repeatedly reported that poor air quality impacts human health. Multiple studies have confirmed associations between non-accidental hospitalisation and periods of increased ambient air pollution (Ab Manan et al., 2018). The majority of studies have investigated respiratory effects, with a meta-analysis finding vehicle emissions to significantly increase the risk of developing asthma in childhood (Khreis et al., 2017), and researchers reporting that PM is particularly hazardous to Chronic Obstructive Pulmonary Disease patients (Choi et al., 2018). Moreover, Zanobetti et al. (2009) found a 2.07% increase in hospitalisation for respiratory diseases with a 10 $\mu g/m^3$ increase in ambient $PM_{2.5}$ concentration (Zanobetti et al., 2009). Concordantly, the American Cancer Society and Pope et al. (2002) found exposure to a 10 $\mu g/m^3$ increase in ambient PM concentration to be associated with a 4%, 6% and 8% increase in all-cause, cardiopulmonary or lung cancer mortality, respectively (Pope et al., 2002). This has led some researchers to conclude that there may be no safe level of air pollution (Zhao et al., 2020).

The mechanism of this respiratory toxicity has been extensively investigated *in vitro* and *in vivo* (see reviews (Cho et al., 2018; Losacco and Perillo, 2018)). Jalava et al. (2007) cultured alveolar macrophages with ambient air pollution from six European cities and consistently found significant decreases in cell viability and increases in tumour necrosis factor alpha (TNF-α) production compared to controls (Jalava et al., 2007). In corroboration, Huang et al. (2008) found TNF-α production to increase in the bronchioalveolar lavage of rats exposed to ambient $PM_{2.5}$ from Beijing, China, and also indicated that phagocytic function is impaired in collected macrophages (Huang et al., 2008). Impaired phagocytosis was also demonstrated by Sigaud et al. (2007) in murine macrophages and neutrophils exposed to concentrated air pollution particles, however, the researchers reported that this required lung priming with interferon-gamma (Sigaud et al., 2007). Moreover, $PM_{2.5}$ has been shown to induce reactive oxygen species (ROS) production (Weichenthal et al., 2013), which has been implicated in mitochondrial dysfunction and hence respiratory damage in human bronchial epithelial cells (Jin et al., 2018). Ultimately, the loss of function of homeostatic immune cells, along with toxicity to resident pulmonary cells suggests that air pollution is damaging to the respiratory system. Hence, epidemiological, *in vitro* and *in vivo* studies have established the effects of air pollution on general health and the respiratory system.

3.2. Bushfire PM

Interestingly, the epidemiological association of air pollution and hospitalisation is not well established in Australia, with two studies failing to find a strong association (Meszaros et al., 2015; Salimi et al., 2018). However, bushfire PM exposure appears to correlate with hospitalisation. A study completed in Darwin, Australia, found an association between bushfire PM exposure and admissions to hospital for respiratory impairment (Crabbe, 2012). Additionally, a study completed in Sydney, Australia, found respiratory hospital admissions to increase by 1.24% with each 10 $\mu g/m^3$ increase in bushfire PM concentration (Morgan et al., 2010). This could suggest that bushfire smoke is the prominent air pollution component that poses as a health threat in Australia.

Studies on bushfire PM have found it to be toxic, pro-inflammatory and suppress macrophage phagocytic function (Franzi et al., 2011; Hamon et al., 2018) (Table 1). Franzi et al. (2011) found bushfire smoke collected during a California, USA bushfire (wildfire) to be toxic to RAW 264.7 macrophages, and concluded that the majority of the cytotoxic effect was as a result of oxidative stress (Franzi et al., 2011; Williams et al., 2013). This aligns with findings from Hamon et al. (2018), who found bushfire smoke to be pro-inflammatory and inhibit phagocytic function in macrophages *in vitro* (Hamon et al., 2018). In a respiratory context, Pavagadhi et al. (2013), found increased apoptosis in a human lung epithelial cell line upon bushfire $PM_{2.5}$ exposure (Pavagadhi et al., 2013), and Williams et al. (2013), found rapid cytotoxicity in alveolar macrophages exposed to wildfire PM (Williams et al., 2013).

Relative to ambient PM, bushfire PM has been found to be more toxic to pulmonary cells, and to induce a greater oxidative stress response. In

Table 1
Toxicity of bushfire PM.

Study	Bushfire PM	Effect	Reference
RAW 264.7 macrophages	California bushfire	Toxicity, oxidative stress, pro-inflammatory activity	Franzi et al. (2011)
Monocyte-derived and THP-1 macrophages	Burning of mixed biomass	Pro-inflammatory activity, suppression of macrophage phagocytic activity	Hamon et al. (2018)
A549 human epithelial respiratory cell line	Singaporean smoke haze episodes	Decreased cell viability	Pavagadhi et al. (2013)
Mouse alveolar macrophages	California bushfire	Cytotoxicity, oxidative stress	Williams et al. (2013)
Mouse bronchioalveolar lavage fluid	Burning of multiple tree species	Lung toxicity and mutagenicity	Kim Yong et al. (2018)
Mouse lung slices	California peat fires	Pro-inflammatory cytokine production	Kim et al. (2014)

fact, Franzi et al. (2011) indicated that bushfire PM was approximately five times more toxic to RAW 264.7 macrophages than ambient PM (Franzi et al., 2011). Kim Yong et al. (2018) investigated the toxicity of woodfire smoke on mouse bronchioalveolar lavage extracts and compared it to published toxicity of different PM sources. They found the woodfire smoke to be more toxic to lung cells than ambient PM from vehicle emissions and even plastic burning (Kim Yong et al., 2018). Additionally, Nakayama-Wong et al. (2011) compared the bronchial epithelial cell toxicity of ambient PM and bushfire PM, and found bushfire PM to elicit greater free radical generation than ambient PM (Nakayama-Wong et al., 2011). This free radical generation is supported by Karthikeyan et al. (2006) who investigated the chemical composition of bushfire smoke, and found a higher proportion of hydroxyl radicals compared to ambient air, and concluded that these could cause oxidative stress (Karthikeyan et al., 2006). Hence, it appears that bushfire PM induces toxicity and a greater oxidative stress response in lung cells than ambient PM.

The greater oxidative stress response due to bushfire PM as compared to ambient PM (Franzi et al., 2011; Karthikeyan et al., 2006; Nakayama-Wong et al., 2011) may be due to the higher proportion of PAH in bushfire smoke (Reyes et al., 2018; Wentworth et al., 2018). PAH and PAH-derived quinones have been linked to oxidative stress in bronchiolar cells (Gurbani et al., 2013), bronchioalveolar cells (Tacka and Penning, 2006), and murine lungs (Rouse et al., 2008). Hence, as PAH is associated with oxidative stress and bushfire PM has a greater level of PAH than ambient PM, it seems that PAH contributes to the unique toxicity of bushfire PM. Of course, other elements not discussed here may have compounding effects, such as organic carbon content (Ntziachristos et al., 2007) or elemental carbon concentration (Alessandrini et al., 2009). Overall, bushfire smoke is toxic to the respiratory system, causing greater oxidative stress than ambient PM, and is associated with hospitalisation for respiratory impairments. Ultimately, the effect of ambient and bushfire PM on general health and specifically respiration is reasonably well known. However, other systems may be impacted by PM, as ambient PM has been demonstrated to enter the brain.

4. Pollutants in the brain

4.1. Extrapulmonary entry route

While bushfire smoke has not currently been demonstrated to enter the brain, multiple brain entry routes for ambient PM, particularly for $PM_{2.5}$ and UFP, have been described. It has been reported that UFP can undergo extrapulmonary travel after inhalation and alveolar deposition (Kreyling et al., 2002; Nemmar et al., 2002; Oberdorster et al., 2002), and that pulmonary inflammation caused by $PM_{2.5}$ may increase the permeability of vascular endothelium in the lungs, leading to systemic circulation of $PM_{2.5}$ (Dai et al., 2016; Yue et al., 2019). However, the ability to cross the gas-blood barrier has been contested by Bräuner et al. (2009), who found no change in permeability with inhaled $PM_{2.5}$ (Bräuner et al., 2009). This may be due to the low, 24-h exposure to high levels of $PM_{2.5}$, leading to lower inflammation and hence less altered permeability. However, further research is required to clarify this process.

If $PM_{2.5}$ and UFP do enter the bloodstream as suggested, they may initiate systemic inflammation, increasing the permeability of the blood-brain barrier (BBB). Systemic inflammation was observed in rats exposed to diesel emission pollution, with high levels of blood IL-6 and TNF-α 24 h post exposure (Robertson et al., 2012). In humans, Li et al. (2017) found that those exposed to air pollution in Boston, USA had increased systemic IL-6 compared to those less exposed (Li et al., 2017), and Delfino et al. (2010) found prolonged exposure to $PM_{2.5}$ to be associated with increased IL-6 plasma concentrations (Delfino et al., 2010). Additionally, blood C reactive protein (CRP) has been shown to be higher in humans exposed to greater air pollution (Lanki et al., 2015). Systemic inflammation, and CRP specifically, has been shown to increase the permeability of the BBB (Elwood et al., 2017; Hsuchou et al., 2012), possibly allowing circulating air pollution to enter the brain. Importantly, it is possible that the increased circulating CRP and IL-6 is instead a by-product of neuroinflammation, and not a precursor to air pollution entering the brain. However, rat studies suggest that the administration may increase systemic inflammation under controlled settings (Robertson et al., 2012). Hence, it is likely that air pollution can cross both the gas-blood barrier and the blood-brain barrier to enter the brain, though continuing research is required to validate this route of entry.

4.2. Olfactory entry route

Interestingly, air pollution is postulated to traverse olfactory neurons by entering at the afferent olfactory pathway to reach the brain. Oberdörster et al. (2004) demonstrated that rats exposed to inhaled UFP had increased PM deposits in multiple brain areas, most significantly the olfactory bulb (Oberdorster et al., 2004). This was later supported by Elder et al. (2006), who found rodents exposed to UFP for 12-days to have greater accumulation of PM in the olfactory bulb than the lungs (Elder et al., 2006). The authors suggested that this could indicate that the olfactory neurons are utilised to translocate particles to the brain. Further investigation by Calderón-Garcidueñas et al. (2010) revealed that PM can be found in olfactory bulb neurons in humans from the heavily polluted Mexico City (Calderón-Garcidueñas et al., 2010). Calderón-Garcidueñas et al. (2008) also identified UFP in the autopsied frontal cortex of a seemingly healthy 27 year old man that lived in the polluted Mexico City (Calderón-Garcidueñas et al., 2008). Concordantly, Maher et al. (2016) have demonstrated the presence of magnetite particles, small magnetic particles thought to be an air pollution constituent, in brain tissue of autopsied humans (Maher et al., 2016). Taken together, it is likely that ambient PM can traverse the olfactory neurons or undertake extrapulmonary travel to reach the brain.

4.3. Bushfire PM entry into brain?

While no evidence has yet emerged for bushfire smoke entry to the brain (most likely due to the lack of studies), it is clear that $PM_{2.5}$ and UFP may enter the brain (Fig. 2). As much of the bushfire PM fits within these size restrictions, it could be postulated that bushfire PM can enter the brain in a similar manner to ambient PM. For example, the majority of PAH was found to be associated with particles of 0.43–2.1 μm in diameter in a study of air pollution in China (Wu et al., 2006), suggesting that PAH could enter the brain. However, further research will be required to confirm this postulation.

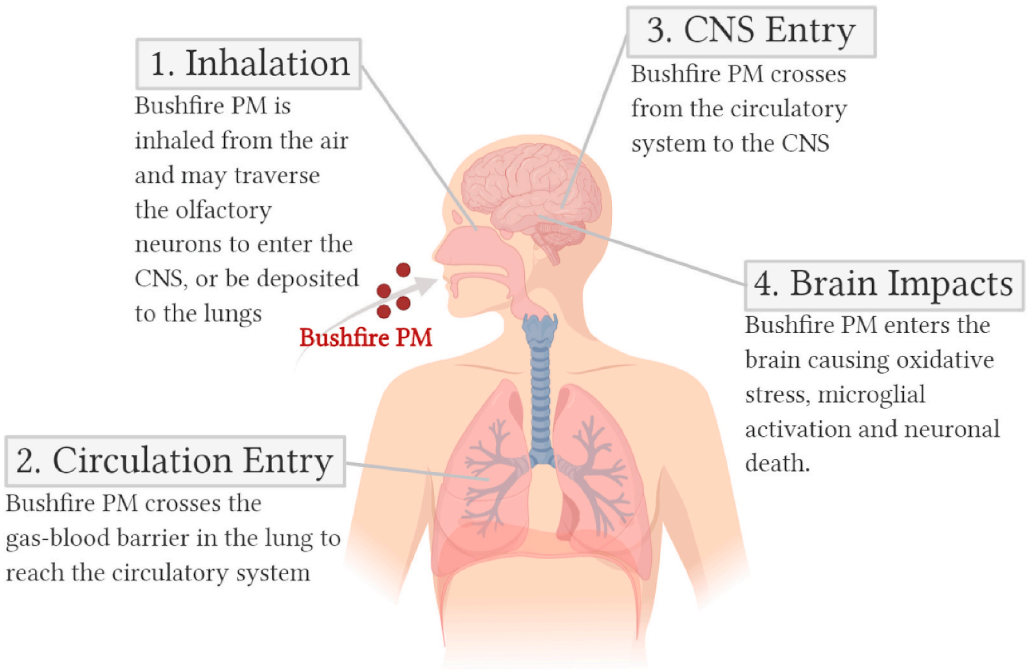

Fig. 2. Postulated entry of bushfire particulate matter into the brain. PM: particulate matter. Image created using BioRender.com.

5. Neurotoxicity of air pollutants

5.1. Ambient PM: in vitro and in vivo studies

Once in the brain, PM is postulated to cause oxidative toxicity and inflammation by interacting with neurons and supporting cells (Table 2). $PM_{2.5}$ was shown to cause oxidative toxicity in rats when up to 10 μg/mL of $PM_{2.5}$ was incubated on homogenised olfactory bulb, cerebral cortex, striatum, hippocampus and cerebellum (Fagundes et al., 2015). All studied concentrations led to severe oxidative stress and lipid peroxidation in the cerebellum and hippocampus, whilst other brain regions appeared unaffected (Fagundes et al., 2015). Additionally, rats intrathecally administered with $PM_{2.5}$ showed a concentration-dependent increase in neural oxidative damage (Zhang et al., 2018). The same study found severe cortical damage in rats exposed to $PM_{2.5}$, characterised by necrotic neurons, gliosis, vasodilation and caspase 3 and 9 activation (Zhang et al., 2018). This damage often leads to inflammation, which Campbell et al. (2005) demonstrated with an increase in TNF-α and IL-1 in the cortex of mice exposed to ambient PM from a Los Angeles highway (Campbell et al., 2005). Woodward et al. (2017) then postulated the inflammation to be mediated by toll-like receptor 4 (TLR-4) on the glial immune cell, microglia. The authors demonstrated that knocking out TLR-4 led to decreased microglial release of TNF-α and other pro-inflammatory cytokines with $PM_{2.5}$ administration (Woodward et al., 2017). Interestingly, Gerlofs-Nijland et al. (2010) demonstrated that the inflammatory response depends greatly on the brain region studied, finding that TNF-α and IL-1α were increased in the striatum of the rat brain after inhalation exposure to diesel PM, but not in the cerebellum, frontal cortex, hippocampus, olfactory bulb or tubercles (Gerlofs-Nijland et al., 2010). This is consistent with the findings that oxidative stress extent depends on brain region, presented by Fagundes et al. (2015) previously, and suggests that the effect on the brain is dependent on location. This could be due to the route of entry, the presence or absence of immune cells, or other factors. Despite the differences, air pollution can cause damage to brain sections, which may explain its association with a myriad of neurological disorders.

Table 2
Neurotoxic effects of air pollution.

Study	Pollution	Effect	Reference
Rat brain regions	Ambient $PM_{2.5}$ from Brazil	Oxidative stress, lipid peroxidation	Fagundes et al. (2015)
Rat neurons	Ambient $PM_{2.5}$ from China	Oxidative damage, necrotic neurons, gliosis	Zhang et al. (2018)
Mouse cortex	Los Angeles highway $PM_{2.5}$	Increased pro-inflammatory cytokines	Campbell et al. (2005)
Rat brain regions	Diesel PM	Increased pro-inflammatory cytokines	Gerlofs-Nijland et al. (2010)
Rat mesencephalic neuron-glia cultures	Diesel PM	Neurotoxicity, reactive oxygen species generation, microglial activation	Block et al. (2004)
Rat brain	Rickshaw engine PM	Neuronal loss	Ejaz et al. (2014)
Primary cortical neuron culture and a neuroblastoma line	Micropollutant benzo[a]pyrene	Neuronal death by microglial activation	Dutta et al. (2010)
Mouse neural slices	Los Angeles freeway PM	Reduction of synaptic function	Davis et al. (2013)

5.2. Ambient PM: epidemiological studies

Studies have noted that periods of elevated ambient air pollution can increase the likelihood of migraines (Lee et al., 2018), stroke (Fu et al., 2019) and dementia (Fu et al., 2019; Kioumourtzoglou et al., 2016). The reports of an association between neurodegenerative diseases like dementia and ambient PM are many. A systemic review of 13 papers found an association between ambient $PM_{2.5}$ exposure and dementia incidence across five countries (Peters et al., 2019), and Calderón-Garcidueñas et al. (2003) demonstrated increased neuroinflammation, a hallmark sign of neurodegeneration, in canines exposed to Mexico City pollution compared to those from rural villages (Calderon-Garciduenas et al., 2003). Calderón-Garcidueñas et al. (2012) also investigated autopsy samples from pollution-exposed children, and found 51% to have diffuse

amyloid plaques in the frontal cortex, compared to 0% for lesser exposed controls (Calderon-Garciduenas et al., 2012). This early AD pathology, usually only present in old age, suggests that air pollution could play a key role in neurodegenerative diseases.

Moreover, a meta-analysis found a strong correlation between $PM_{2.5}$ exposure and depression and suicide (Gładka et al., 2018), and a study of 54 000 Danes found a correlation between exposure and brain cancer risk (Raaschou-Nielsen et al., 2011). It is important to emphasise that epidemiological associations do not indicate causation. In fact, when the Danish study was followed up by the same research group, a correlation was not found between exposure and brain tumours, though this is likely due to the smaller sample size in this study (Poulsen et al., 2016). Conversely, a meta-analysis concluded that there may be mounting evidence of a causal relationship between air pollution exposure and autism (Weisskopf et al., 2015). Taken together, these associations indicate that exposure to air pollution may increase the risk of many neurological disorders, especially when reports of elevated oxidative stress and neuroinflammation are considered.

5.3. Bushfire PM: postulated effect

Studies investigating the effect of bushfire smoke on brain health are limited and the authors are unaware of any studies exposing neural cells to bushfire smoke *in vitro*, or studies investigating the effect of bushfire smoke on the brain *in vivo*. However, it is possible to postulate that bushfire PM can have an effect on brain health. Firstly, it appears clear that air pollution can, and has, entered the brain, so it is likely that bushfire PM less than 2.5 μm may enter through an extrapulmonary route, or via the olfactory neurons. Secondly, ambient PM has been reported to be toxic to both respiratory and neural cells. Whilst bushfire smoke has only been investigated in respiratory cells, it induced similar, if not greater toxicity and oxidative stress responses than ambient PM. Hence, it is reasonable to postulate that bushfire smoke may be toxic to neural cells in the same way. Finally, bushfire smoke has been demonstrated to impair immune cells and be pro-inflammatory (Hamon et al., 2018; Williams et al., 2013). The brain tissue resident macrophage, microglia, play a key role in homeostasis of the brain, preventing uncontrolled inflammation, and responding to insults (Gogoleva et al., 2019). If bushfire PM entered the brain and modulated the resident immune cells, the effect could be unregulated brain inflammation (Fig. 3). This has been associated with multiple neurodegenerative diseases (Guzman-Martinez et al., 2019). Hence, it is possible that bushfire smoke may enter the brain, cause damage to cells and modulate brain immunology. However, no *in vitro* or *in vivo* experiments have been published for these effects, so much greater research is required. Epidemiological evidence, however, does support this argument, by showing that there may be an association between fire-derived smoke and neurological disorders.

5.4. Bushfire PM: epidemiological evidence

Epidemiological studies provide correlational evidence of an association between fire-derived PM exposure and some neurological disorders. These studies primarily focus on residential wood burning, such as that in fireplaces, wood heaters, or open-fire cooking. This is a major source of air pollution, even in industrial countries (Szidat et al., 2007), and may serve as a proxy for bushfire PM, though does not completely capitulate the components of bushfire smoke. Oudin et al. (2018) investigated dementia incidence and exposure to air pollution from residential wood burning in Northern Sweden, and found an association between the two (Oudin et al., 2018). Additionally, Munroe and Gauvain et al. (2012) found a correlation between exposure to open-fire cooking and decreased cognitive ability in children (Munroe and Gauvain, 2012), and Banjeree et al. (2012) found Indian women exposed to woodfire smoke from indoor biomass burning to have increased depression (Banerjee et al., 2012). Interestingly, Greenop et al. (2015) investigated parental exposure to indoor woodfire heating, and found that paternal exposure led to increased incidence of brain tumours in offspring in Australia (Greenop et al., 2015), possibly suggesting that woodfire can genetically mutate neural components. Hence, there appears to be a correlation between smoke exposure and neurological disorders.

Taken together, this line of evidence suggests that bushfire PM may be toxic to neural cells as seen with ambient PM, and that epidemiologically, bushfire PM may be associated with neural disease. Hence, it is important to further this research, and understand the effect of bushfire PM on the brain, before bushfire PM is observed more often.

5.5. Australia at risk and what this means for worldwide wildfire health impacts

No studies to date have investigated the effect of bushfire smoke on brain health in Australia. This is of key importance, as the type of biomass burnt may drastically alter the impact on the brain. Some studies suggest that smoke from bushfires, especially that involving the Australian native, eucalyptus, is more toxic to mouse pulmonary cells than air pollution from vehicles (Kim Yong et al., 2018). The study found smoke from eucalyptus to have the highest lung toxicity compared to pine, pine needles, peat and red oak (Kim Yong et al., 2018). This could indicate that Australian bushfire smoke has unique toxicity, that requires further investigation especially in the context of brain health.

Critically, the effect of long-term exposure to bushfire smoke, as seen

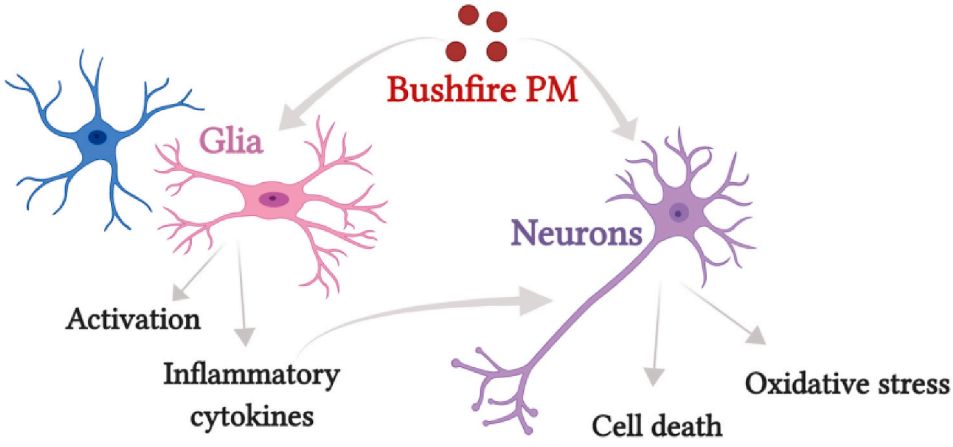

Fig. 3. Postulated impact of bushfire particulate matter in the brain. Glia includes microglia and astrocytes. PM: particulate matter. Image created using BioRender.com.

in Australia in recent months, is unknown. Recent studies have investigated the long term effects of ambient air pollution, with a longitudinal study of 998 females finding prolonged exposure to PM to lead to accelerated cognitive decline (Younan et al., 2019), and a cohort study of 117 575 Chinese participants finding an increased likelihood of stroke with prolonged $PM_{2.5}$ exposure (Huang et al., 2019). Moreover, a pilot study in mice revealed that 9-month $PM_{2.5}$ exposure led to increased Alzheimer's Disease-like pathology in the brain compared to control mice (Bhatt et al., 2015). Given that ambient PM and bushfire PM likely have similar pathological effects, as seen in lung epithelia and macrophages, it could be postulated that exposure to bushfire smoke may be equally as damaging to the brain in the long term. This could have immense consequences on the brain health of Australians, as bushfire smoke is predicted to become a more common occurrence.

Additionally, bushfire smoke often undergoes long-range transport from the frontline and settles on nearby cities (Nogrady, 2019). Whilst studies have shown this time in the air to chemically transform the organic fraction of smoke and decrease toxicity, it appears that the general increase in PM concentration in these cities is most damaging (Jalava et al., 2006). Overall, the complexity of long-range transport of smoke remains unsolved and could be of importance when investigating the effects of bushfires on the general population.

Moreover, the full effect on developing children is unknown, and as the bushfire smoke covers more Australian cities, more children may be affected. In rats, the exposure to traffic-associated PM from birth meant that at 5 months of age, the exposed rats had 70% less newly generated neurons in the hippocampus compared to controls, and had activated microglia and a more permeable blood-brain barrier (Woodward et al., 2018). This suggests the developmental impairment of brain structures which could impair normal brain function. An epidemiological study of children from the Netherlands found reduced cerebral cortex in the brains of those more exposed to ambient PM, and suggested the associated cognitive impairment could have drastic long-term effects (Guxens et al., 2018). Moreover, Calderón-Garcidueñas et al. (2011) found children exposed to air pollutants due to residing in a highly polluted city had increased risk for auditory and vestibular impairment compared to controls (Calderon-Garciduenas et al., 2011). If bushfire PM has similar effects to ambient PM, the high levels of bushfire smoke may alter the development of many Australian children.

The danger of bushfire PM is not only limited to Australia. Many cities worldwide experience yearly bushfires (wildfires or forest fires) or grass fires, and many of their surrounding cities are exposed to bushfire PM at those times. In the US, tens of thousands of bushfires rage yearly, with Western bushfires, like those observed in California, being the largest (Congressional Research Service, 2019). Concerningly, the incidence of California wildfires has been predicted to increase with the rise of climate change (Westerling et al., 2011). Moreover, hundreds to tens of thousands of bushfires have been reported to burn in each European country in 2018 (European Forest Fire Information System, 2018), exposing much of the continent to bushfire PM. Asia is also at risk, with fires like those often seen in Indonesia being found to impact neighbouring Singapore (Sheldon and Sankaran, 2017), and fire damaging over half of Southern Asia from 2003 to 2017 (Reddy et al., 2020). Using Australia as an example, it is clear that bushfire PM may be extremely damaging to brain health in the bushfire season. Considerably more research is required to understand these effects, as climate change predictions become increasingly threatening and the incidence of bushfire PM exposure is set to increase.

Taking action

Bushfire smoke is postulated to have significant effects on brain health, and if this problem is not promptly addressed, we may see the long-term effects of bushfire smoke earlier than we imagined. Hence, further research into the effects of bushfire smoke on brain health and disease will be instrumental in preventing population-wide health effects. Importantly, increasing the understanding of these effects will allow the translation to legislative changes and public health campaigns. For now, people should be made aware of the possible dangers of bushfire smoke, both in a respiratory and brain health context, and urged to limit their exposure to bushfire PM. This can be achieved by remaining indoors with air-conditioning to filter the air, and, if they choose to wear a mask, ensuring it is a properly fitted P2. Future investigations must prioritise the understanding of the effects of bushfire smoke on brain health, as the bushfire season seems to be here to stay.

Funding

A.R.W is a recipient of an NHMRC Senior Research Fellowship (APP1118452).

References

Ab Manan, N., Noor Aizuddin, A., Hod, R., 2018. Effect of air pollution and hospital admission: a systematic review. Annals of global health 84, 670–678.
Alessandrini, F., Beck-Speier, I., Krappmann, D., Weichenmeier, I., Takenaka, S., Karg, E., Kloo, B., Schulz, H., Jakob, T., Mempel, M., Behrendt, H., 2009. Role of oxidative stress in ultrafine particle–induced exacerbation of allergic lung inflammation. Am. J. Respir. Crit. Care Med. 179, 984–991.
Banerjee, M., Siddique, S., Dutta, A., Mukherjee, B., Ranjan Ray, M., 2012. Cooking with biomass increases the risk of depression in pre-menopausal women in India. Soc. Sci. Med. 75, 565–572.
Bhatt, D.P., Puig, K.L., Gorr, M.W., Wold, L.E., Combs, C.K., 2015. A pilot study to assess effects of long-term inhalation of airborne particulate matter on early Alzheimer-like changes in the mouse brain. PloS One 10, e0127102.
Block, M.L., Wu, X., Pei, Z., Li, G., Wang, T., Qin, L., Wilson, B., Yang, J., Hong, J.S., Veronesi, B., 2004. Nanometer size diesel exhaust particles are selectively toxic to dopaminergic neurons: the role of microglia, phagocytosis, and NADPH oxidase. Faseb. J. 18, 1618–1620.
Bräuner, E.V., Mortensen, J., Møller, P., Bernard, A., Vinzents, P., Wåhlin, P., Glasius, M., Loft, S., 2009. Effects of ambient air particulate exposure on blood–gas barrier permeability and lung function. Inhal. Toxicol. 21, 38–47.
Calderon-Garciduenas, L., D'Angiulli, A., Kulesza, R.J., Torres-Jardon, R., Osnaya, N., Romero, L., Keefe, S., Herritt, L., Brooks, D.M., Avila-Ramirez, J., Delgado-Chavez, R., Medina-Cortina, H., Gonzalez-Gonzalez, L.O., 2011. Air pollution is associated with brainstem auditory nuclei pathology and delayed brainstem auditory evoked potentials. Int. J. Dev. Neurosci. 29, 365–375.
Calderón-Garcidueñas, L., Franco-Lira, M., Henríquez-Roldán, C., Osnaya, N., González-Maciel, A., Reynoso-Robles, R., Villarreal-Calderon, R., Herritt, L., Brooks, D., Keefe, S., Palacios-Moreno, J., Villarreal-Calderon, R., Torres-Jardón, R., Medina-Cortina, H., Delgado-Chávez, R., Aiello-Mora, M., Maronpot, R.R., Doty, R.L., 2010. Urban air pollution: influences on olfactory function and pathology in exposed children and young adults. Exp. Toxicol. Pathol. 62, 91–102.
Calderon-Garciduenas, L., Kavanaugh, M., Block, M., D'Angiulli, A., Delgado-Chavez, R., Torres-Jardon, R., Gonzalez-Maciel, A., Reynoso-Robles, R., Osnaya, N., Villarreal-Calderon, R., Guo, R., Hua, Z., Zhu, H., Perry, G., Diaz, P., 2012. Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques, and down-regulation of the cellular prion protein in air pollution exposed children and young adults. J. Alzheim. Dis. : JAD 28, 93–107.
Calderon-Garciduenas, L., Maronpot, R.R., Torres-Jardon, R., Henriquez-Roldan, C., Schoonhoven, R., Acuna-Ayala, H., Villarreal-Calderon, A., Nakamura, J., Fernando, R., Reed, W., Azzarelli, B., Swenberg, J.A., 2003. DNA damage in nasal and brain tissues of canines exposed to air pollutants is associated with evidence of chronic brain inflammation and neurodegeneration. Toxicol. Pathol. 31, 524–538.
Calderón-Garcidueñas, L., Solt, A.C., Henríquez-Roldán, C., Torres-Jardón, R., Nuse, B., Herritt, L., Villarreal-Calderón, R., Osnaya, N., Stone, I., García, R., Brooks, D.M., González-Maciel, A., Reynoso-Robles, R., Delgado-Chávez, R., Reed, W., 2008. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid β-42 and α-synuclein in children and young adults. Toxicol. Pathol. 36, 289–310.
Campbell, A., Oldham, M., Becaria, A., Bondy, S.C., Meacher, D., Sioutas, C., Misra, C., Mendez, L.B., Kleinman, M., 2005. Particulate matter in polluted air may increase biomarkers of inflammation in mouse brain. Neurotoxicology 26, 133–140.
Cho, C.-C., Hsieh, W.-Y., Tsai, C.-H., Chen, C.-Y., Chang, H.-F., Lin, C.-S., 2018. In vitro and in vivo experimental studies of PM(2.5) on disease progression. Int. J. Environ. Res. Publ. Health 15, 1380.
Choi, J., Oh, J.Y., Lee, Y.S., Min, K.H., Hur, G.Y., Lee, S.Y., Kang, K.H., Shim, J.J., 2018. Harmful impact of air pollution on severe acute exacerbation of chronic obstructive pulmonary disease: particulate matter is hazardous. Int. J. Chronic Obstr. Pulm. Dis. 13, 1053–1059.
Congressional Research Service, 2019. Wildfire statistics. https://crsreports.congress.gov/product/pdf/IF/IF10244 (accessed 5 February 2020).
Crabbe, H., 2012. Risk of respiratory and cardiovascular hospitalisation with exposure to bushfire particulates: new evidence from Darwin, Australia. Environ. Geochem. Health 34, 697–709.

Dai, J., Sun, C., Yao, Z., Chen, W., Yu, L., Long, M., 2016. Exposure to concentrated ambient fine particulate matter (PM2.5) disrupts vascular endothelial cell barrier function via the IL-6/HIF-1α signaling pathway. FEBS Open Bio 6.
Davis, D.A., Akopian, G., Walsh, J.P., Sioutas, C., Morgan, T.E., Finch, C.E., 2013. Urban air pollutants reduce synaptic function of CA1 neurons via an NMDA/NÒ pathway in vitro. J. Neurochem. 127, 509–519.
De Vos, A.J.B.M., Reisen, F., Cook, A., Devine, B., Weinstein, P., 2009. Respiratory irritants in Australian bushfire smoke: air toxics sampling in a smoke chamber and during prescribed burns. Arch. Environ. Contam. Toxicol. 56, 380–388.
Delfino, R.J., Staimer, N., Tjoa, T., Arhami, M., Polidori, A., Gillen, D.L., George, S.C., Shafer, M.M., Schauer, J.J., Sioutas, C., 2010. Associations of primary and secondary organic aerosols with airway and systemic inflammation in an elderly panel cohort. Epidemiology 21, 892–902.
Dutta, K., Ghosh, D., Nazmi, A., Kumawat, K.L., Basu, A., 2010. A common carcinogen benzo[a]pyrene causes neuronal death in mouse via microglial activation. PloS One 5, e9984.
Ejaz, S., Anwar, K., Ashraf, M., 2014. MRI and neuropathological validations of the involvement of air pollutants in cortical selective neuronal loss. Environ. Sci. Pollut. Control Ser. 21, 3351–3362.
Elder, A., Gelein, R., Silva, V., Feikert, T., Opanashuk, L., Carter, J., Potter, R., Maynard, A., Ito, Y., Finkelstein, J., Oberdorster, G., 2006. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environ. Health Perspect. 114, 1172–1178.
Elwood, E., Lim, Z., Naveed, H., Galea, I., 2017. The effect of systemic inflammation on human brain barrier function. Brain Behav. Immun. 62, 35–40.
European Forest Fire Information System, 2018. Forest fires in europe, Middle East and North africa 2018. https://effis.jrc.ec.europa.eu/media/cms_page_media/40/Annual_Report_2018_final_pdf_06.11.2019_n208KFB.pdf (accessed 5 February 2020).
Fagundes, L.S., Fleck Ada, S., Zanchi, A.C., Saldiva, P.H., Rhoden, C.R., 2015. Direct contact with particulate matter increases oxidative stress in different brain structures. Inhal. Toxicol. 27, 462–467.
Frampton, M.W., Rich, D.Q., 2016. Does particle size matter? Ultrafine particles and hospital visits in eastern europe. Am. J. Respir. Crit. Care Med. 194, 1180–1182.
Franzi, L.M., Bratt, J.M., Williams, K.M., Last, J.A., 2011. Why is particulate matter produced by wildfires toxic to lung macrophages? Toxicol. Appl. Pharmacol. 257, 182–188.
Fu, P., Guo, X., Cheung, F.M.H., Yung, K.K.L., 2019. The association between PM2.5 exposure and neurological disorders: a systematic review and meta-analysis. Sci. Total Environ. 655, 1240–1248.
Gerlofs-Nijland, M.E., van Berlo, D., Cassee, F.R., Schins, R.P.F., Wang, K., Campbell, A., 2010. Effect of prolonged exposure to diesel engine exhaust on proinflammatory markers in different regions of the rat brain. Part. Fibre Toxicol. 7, 12-12.
Gładka, A., Rymaszewska, J., Zatoński, T., 2018. Impact of air pollution on depression and suicide. Int. J. Occup. Med. Environ. Health 31, 711–721.
Gogoleva, V.S., Drutskaya, M.S., Atretkhany, K.S., 2019. [The role of microglia in the homeostasis of the central nervous system and neuroinflammation]. Mol. Biol. 53, 790–798.
Greenop, K.R., Hinwood, A.L., Fritschi, L., Scott, R.J., Attia, J., Ashton, L.J., Heath, J.A., Armstrong, B.K., Milne, E., 2015. Vehicle refuelling, use of domestic wood heaters and the risk of childhood brain tumours: results from an Australian case–control study. Pediatr. Blood Canc. 62, 229–234.
Gurbani, D., Bharti, S.K., Kumar, A., Pandey, A.K., Ana, G.R., Verma, A., Khan, A.H., Patel, D.K., Mudiam, M.K., Jain, S.K., Roy, R., Dhawan, A., 2013. Polycyclic aromatic hydrocarbons and their quinones modulate the metabolic profile and induce DNA damage in human alveolar and bronchiolar cells. Int. J. Hyg Environ. Health 216, 553–565.
Guxens, M., Lubczyńska, M.J., Muetzel, R.L., Dalmau-Bueno, A., Jaddoe, V.W.V., Hoek, G., van der Lugt, A., Verhulst, F.C., White, T., Brunekreef, B., Tiemeier, H., El Marroun, H., 2018. Air pollution exposure during fetal life, brain morphology, and cognitive function in school-age children. Biol. Psychiatr. 84, 295–303.
Guzman-Martinez, L., Maccioni, R.B., Andrade, V., Navarrete, L.P., Pastor, M.G., Ramos-Escobar, N., 2019. Neuroinflammation as a common feature of neurodegenerative disorders. Front. Pharmacol. 10.
Hamon, R., Tran, H.B., Roscioli, E., Ween, M., Jersmann, H., Hodge, S., 2018. Bushfire smoke is pro-inflammatory and suppresses macrophage phagocytic function. Sci. Rep. 8, 13424.
Hoek, G., Pattenden, S., Willers, S., Antova, T., Fabianova, E., Braun-Fahrländer, C., Forastiere, F., Gehring, U., Luttmann-Gibson, H., Grize, L., Heinrich, J., Houthuijs, D., Janssen, N., Katsnelson, B., Kosheleva, A., Moshammer, H., Neuberger, M., Privalova, L., Rudnai, P., Speizer, F., Slachtova, H., Tomaskova, H., Zlotkowska, R., Fletcher, T., 2012. PM_{10}, and children's respiratory symptoms and lung function in the PATY study. Eur. Respir. J. 40, 538.
Hsuchou, H., Kastin, A.J., Mishra, P.K., Pan, W., 2012. C-reactive protein increases BBB permeability: implications for obesity and neuroinflammation. Cell. Physiol. Biochem. : international journal of experimental cellular physiology, biochemistry, and pharmacology 30, 1109–1119.
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., Lu, X., Gu, D., 2019. Long term exposure to ambient fine particulate matter and incidence of stroke: prospective cohort study from the China-PAR project. BMJ 367, l6720.
Huang, K., Liu, G., Zhou, L.-m., Li, J.-h., Xu, H., Wu, D., Hong, L., Chen, H.-y., Yang, W.-z., 2015. Organic carbon and elemental carbon in forest biomass burning smoke. Huan jing ke xue Huanjing kexue 36, 1998–2004.
Huang, N.-H., Wang, Q., Xu, D.-Q., 2008. Immunological effect of PM2.5 on cytokine production in female wistar Rats1 1 This research was supported by the national natural science foundation of China (No. 20077033). Biomed. Environ. Sci. 21, 63–68.
Jalava, P.I., Salonen, R.O., Hälinen, A.I., Penttinen, P., Pennanen, A.S., Sillanpää, M., Sandell, E., Hillamo, R., Hirvonen, M.-R., 2006. In vitro inflammatory and cytotoxic effects of size-segregated particulate samples collected during long-range transport of wildfire smoke to Helsinki. Toxicol. Appl. Pharmacol. 215, 341–353.
Jalava, P.I., Salonen, R.O., Pennanen, A.S., Sillanpää, M., Hälinen, A.I., Happo, M.S., Hillamo, R., Brunekreef, B., Katsouyanni, K., Sunyer, J., Hirvonen, M.-R., 2007. Heterogeneities in inflammatory and cytotoxic responses of RAW 264.7 macrophage cell line to urban air coarse, fine, and ultrafine particles from six European sampling campaigns. Inhal. Toxicol. 19, 213–225.
Jin, X., Xue, B., Zhou, Q., Su, R., Li, Z., 2018. Mitochondrial damage mediated by ROS incurs bronchial epithelial cell apoptosis upon ambient PM 2.5 exposure. J. Toxicol. Sci. 43, 101–111.
Karthikeyan, S., Balasubramanian, R., Iouri, K., 2006. Particulate air pollution from bushfires: human exposure and possible health effects. J. Toxicol. Environ. Health 69 (Part A), 1895–1908.
Khreis, H., Kelly, C., Tate, J., Parslow, R., Lucas, K., Nieuwenhuijsen, M., 2017. Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. Environ. Int. 100, 1–31.
Kim, Y.H., Tong, H., Daniels, M., Boykin, E., Krantz, Q.T., McGee, J., Hays, M., Kovalcik, K., Dye, J.A., Gilmour, M.I., 2014. Cardiopulmonary toxicity of peat wildfire particulate matter and the predictive utility of precision cut lung slices. Part. Fibre Toxicol. 11, 29-29.
Kim Yong, H., Warren Sarah, H., Krantz, Q.T., King, C., Jaskot, R., Preston William, T., George Barbara, J., Hays Michael, D., Landis Matthew, S., Higuchi, M., DeMarini David, M., Gilmour, M.I., 2018. Mutagenicity and lung toxicity of smoldering vs. Flaming emissions from various biomass fuels: implications for health effects from wildland fires. Environ. Health Perspect. 126, 017011.
Kioumourtzoglou, M.A., Schwartz, J.D., Weisskopf, M.G., Melly, S.J., Wang, Y., Dominici, F., Zanobetti, A., 2016. Long-term PM2.5 exposure and neurological hospital admissions in the northeastern United States. Environ. Health Perspect. 124, 23–29.
Kreyling, W.G., Semmler, M., Erbe, F., Mayer, P., Takenaka, S., Schulz, H., Oberdorster, G., Ziesenis, A., 2002. Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. J. Toxicol. Environ. Health 65, 1513–1530.
Kundu, S., Stone, E.A., 2014. Composition and sources of fine particulate matter across urban and rural sites in the Midwestern United States. Environmental science. Processes & impacts 16, 1360–1370.
Lanki, T., Hampel, R., Tiittanen, P., Andrich, S., Beelen, R., Brunekreef, B., Dratva, J., De Faire, U., Fuks, K.B., Hoffmann, B., Imboden, M., Jousilahti, P., Koenig, W., Mahabadi, A.A., Künzli, N., Pedersen, N.L., Penell, J., Pershagen, G., Probst-Hensch, N.M., Schaffner, E., Schindler, C., Sugiri, D., Swart, W.J.R., Tsai, M.-Y., Turunen, A.W., Weinmayr, G., Wolf, K., Yli-Tuomi, T., Peters, A., 2015. Air pollution from road traffic and systemic inflammation in adults: a cross-sectional analysis in the European escape project. Environ. Health Perspect. 123, 785–791.
Lee, H., Myung, W., Cheong, H.K., Yi, S.M., Hong, Y.C., Cho, S.I., Kim, H., 2018. Ambient air pollution exposure and risk of migraine: synergistic effect with high temperature. Environ. Int. 121, 383–391.
Li, W., Dorans, K.S., Wilker, E.H., Rice, M.B., Ljungman, P.L., Schwartz, J.D., Coull, B.A., Koutrakis, P., Gold, D.R., Keaney Jr., J.F., Vasan, R.S., Benjamin, E.J., Mittleman, M. A., 2017. Short-term exposure to ambient air pollution and biomarkers of systemic inflammation: the framingham heart study. Arterioscler. Thromb. Vasc. Biol. 37, 1793–1800.
Liu, J.C., Peng, R.D., 2019. The impact of wildfire smoke on compositions of fine particulate matter by ecoregion in the Western US. J. Expo. Sci. Environ. Epidemiol. 29, 765–776.
Losacco, C., Perillo, A., 2018. Particulate matter air pollution and respiratory impact on humans and animals. Environ. Sci. Pollut. Control Ser. 25, 33901–33910.
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. Proc. Natl. Acad. Sci. Unit. States Am. 113, 10797.
Meszaros, D., Markos, J., FitzGerald, D.G., Walters, E.H., Wood-Baker, R., 2015. An observational study of PM10 and hospital admissions for acute exacerbations of chronic respiratory disease in Tasmania, Australia 1992-2002. BMJ Open Respir Res 2, e000063.
Moller, P., Jacobsen, N.R., Folkmann, J.K., Danielsen, P.H., Mikkelsen, L., Hemmingsen, J.G., Vesterdal, L.K., Forchhammer, L., Wallin, H., Loft, S., 2010. Role of oxidative damage in toxicity of particulates. Free Radic. Res. 44, 1–46.
Morakinyo, O.M., Mokgobu, M.I., Mukhola, M.S., Hunter, R.P., 2016. Health outcomes of exposure to biological and chemical components of inhalable and respirable particulate matter. Int. J. Environ. Res. Publ. Health 13, 592.
Morgan, G., Sheppeard, V., Khalaj, B., Ayyar, A., Lincoln, D., Jalaludin, B., Beard, J., Corbett, S., Lumley, T., 2010. Effects of bushfire smoke on daily mortality and hospital admissions in Sydney, Australia. Epidemiology 21, 47–55.
Munroe, R.L., Gauvain, M., 2012. Exposure to open-fire cooking and cognitive performance in children. Int. J. Environ. Health Res. 22, 156–164.
Nakayama-Wong, L.S., Aung, H.H., Lamé, M.W., Wegesser, T.C., Wilson, D.W., 2011. Fine particulate matter from urban ambient and wildfire sources from California's San Joaquin Valley initiate differential inflammatory, oxidative stress, and xenobiotic responses in human bronchial epithelial cells. Toxicol. Vitro 25, 1895–1905.

Nemmar, A., Hoet, P.H., 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.
Nogrady, B., 2019. Bushfires: Australia issues health warnings as Sydney air quality plummets. BMJ 367, l6914.
Nolan, R.H., Boer, M.M., Collins, L., Resco de Dios, V., Clarke, H., Jenkins, M., Kenny, B., Bradstock, R.A., 2020. Causes and consequences of eastern Australia's 2019–20 season of mega-fires. Global Change Biol. 26, 1039–1041.
Ntziachristos, L., Froines, J.R., Cho, A.K., Sioutas, C., 2007. Relationship between redox activity and chemical speciation of size-fractionated particulate matter. Part. Fibre Toxicol. 4, 5.
Oberdorster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Kreyling, W., Cox, C., 2004. Translocation of inhaled ultrafine particles to the brain. Inhal. Toxicol. 16, 437–445.
Oberdorster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Lunts, A., Kreyling, W., Cox, C., 2002. Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats. J. Toxicol. Environ. Health 65, 1531–1543.
Oudin, A., Segersson, D., Adolfsson, R., Forsberg, B., 2018. Association between air pollution from residential wood burning and dementia incidence in a longitudinal study in Northern Sweden. PloS One 13, e0198283.
Page, S.E., Hooijer, A., 2016. In the line of fire: the peatlands of southeast Asia. Philosophical transactions of the royal society of london. Series B, Biological sciences 371, 20150176.
Pavagadhi, S., Betha, R., Venkatesan, S., Balasubramanian, R., Hande, M.P., 2013. Physicochemical and toxicological characteristics of urban aerosols during a recent Indonesian biomass burning episode. Environ. Sci. Pollut. Control Ser. 20, 2569–2578.
Peters, R., Ee, N., Peters, J., Booth, A., Mudway, I., Anstey, K.J., 2019. Air pollution and dementia: a systematic review. J. Alzheim. Dis. : JAD 70, S145–s163.
Pope 3rd, C.A., Burnett, R.T., Thun, M.J., Calle, E.E., Krewski, D., Ito, K., Thurston, G.D., 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. Jama 287, 1132–1141.
Pöschl, U., 2005. Atmospheric aerosols: composition, transformation, climate and health effects. Angew. Chem. Int. Ed. 44, 7520–7540.
Poulsen, A.H., Sørensen, M., Andersen, Z.J., Ketzel, M., Raaschou-Nielsen, O., 2016. Air pollution from traffic and risk for brain tumors: a nationwide study in Denmark. Canc. Causes Contr. 27, 473–480.
Raaschou-Nielsen, O., Andersen, Z.J., Hvidberg, M., Jensen, S.S., Ketzel, M., Sørensen, M., Hansen, J., Loft, S., Overvad, K., Tjønneland, A., 2011. Air pollution from traffic and cancer incidence: a Danish cohort study. Environ. Health 10, 67.
Reddy, C.S., Bird, N.G., Sreelakshmi, S., Manikandan, T.M., Asra, M., Krishna, P.H., Jha, C.S., Rao, P.V.N., Diwakar, P.G., 2020. Identification and characterization of spatio-temporal hotspots of forest fires in South Asia. Environ. Monit. Assess. 191, 791.
Reyes, J.M., Hubbard, H.F., Stiegel, M.A., Pleil, J.D., Serre, M.L., 2018. Predicting polycyclic aromatic hydrocarbons using a mass fraction approach in a geostatistical framework across North Carolina. J. Expo. Sci. Environ. Epidemiol. 28, 381–391.
Robertson, S., Gray, G.A., Duffin, R., McLean, S.G., Shaw, C.A., Hadoke, P.W.F., 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. Part. Fibre Toxicol. 9, 9-9.
Robinson, M.S., Anthony, T.R., Littau, S.R., Herckes, P., Nelson, X., Poplin, G.S., Burgess, J.L., 2008. Occupational PAH exposures during prescribed pile burns. Ann. Occup. Hyg. 52, 497–508.
Rouse, R.L., Murphy, G., Boudreaux, M.J., Paulsen, D.B., Penn, A.L., 2008. Soot nanoparticles promote biotransformation, oxidative stress, and inflammation in murine lungs. Am. J. Respir. Cell Mol. Biol. 39, 198–207.
Salimi, F., Morgan, G., Rolfe, M., Samoli, E., Cowie, C.T., Hanigan, I., Knibbs, L., Cope, M., Johnston, F.H., Guo, Y., Marks, G.B., Heyworth, J., Jalaludin, B., 2018. Long-term exposure to low concentrations of air pollutants and hospitalisation for respiratory diseases: a prospective cohort study in Australia. Environ. Int. 121, 415–420.
Schraufnagel, D.E., Balmes, J.R., Cowl, C.T., De Matteis, S., Jung, S.-H., Mortimer, K., Perez-Padilla, R., Rice, M.B., Riojas-Rodriguez, H., Sood, A., Thurston, G.D., To, T., Vanker, A., Wuebbles, D.J., 2019. Air pollution and noncommunicable diseases: a review by the forum of international respiratory societies 2019; environmental committee, Part 1: the damaging effects of air pollution. Chest 155, 409–416.
Sheldon, T.L., Sankaran, C., 2017. The impact of Indonesian forest fires on Singaporean pollution and health. Am. Econ. Rev. 107, 526–529.
Sigaud, S., Goldsmith, C.-A.W., Zhou, H., Yang, Z., Fedulov, A., Imrich, A., Kobzik, L., 2007. Air pollution particles diminish bacterial clearance in the primed lungs of mice. Toxicol. Appl. Pharmacol. 223, 1–9.
Spickett, J.T., Brown, H.L., Rumchev, K., 2011. Climate change and air quality: the potential impact on health. Asia Pac. J. Publ. Health 23, 37S–45S.
Steffin, W., Hughes, L., 2013. Be Prepared: Climate Change and the Australian Bushfire Threat. Climate Council of Australia Ltd.
Szidat, S., Prévôt, A.S.H., Sandradewi, J., Alfarra, M.R., Synal, H.-A., Wacker, L., Baltensperger, U., 2007. Dominant impact of residential wood burning on particulate matter in Alpine valleys during winter. Geophys. Res. Lett. 34.
Tacka, K.A., Penning, T.M., 2006. PAH-induced oxidative stress in human lung cells: dependence on functional aldo-keto reductase expression. Canc. Res. 66, 1226.
Vallero, D., 2014. Fundamentals of Air Pollution, fifth ed. Academic Press, California, USA.
Weichenthal, S.A., Godri-Pollitt, K., Villeneuve, P.J., 2013. PM2.5, oxidant defence and cardiorespiratory health: a review. Environ. Health : a global access science source 12, 40.
Weisskopf, M.G., Kioumourtzoglou, M.A., Roberts, A.L., 2015. Air pollution and autism spectrum disorders: causal or confounded? Curr Environ Health Rep 2, 430–439.
Wentworth, G.R., Aklilu, Y.-a., Landis, M.S., Hsu, Y.-M., 2018. Impacts of a large boreal wildfire on ground level atmospheric concentrations of PAHs, VOCs and ozone. Atmos. Environ. 178, 19–30.
Westerling, A.L., Bryant, B.P., Preisler, H.K., Holmes, T.P., Hidalgo, H.G., Das, T., Shrestha, S.R., 2011. Climate change and growth scenarios for California wildfire. Climatic Change 109, 445–463.
Williams, K.M., Franzi, L.M., Last, J.A., 2013. Cell-specific oxidative stress and cytotoxicity after wildfire coarse particulate matter instillation into mouse lung. Toxicol. Appl. Pharmacol. 266, 48–55.
Woodward, N.C., Haghani, A., Johnson, R.G., Hsu, T.M., Saffari, A., Sioutas, C., Kanoski, S.E., Finch, C.E., Morgan, T.E., 2018. Prenatal and early life exposure to air pollution induced hippocampal vascular leakage and impaired neurogenesis in association with behavioral deficits. Transl. Psychiatry 8, 261.
Woodward, N.C., Levine, M.C., Haghani, A., Shirmohammadi, F., Saffari, A., Sioutas, C., Morgan, T.E., Finch, C.E., 2017. Toll-like receptor 4 in glial inflammatory responses to air pollution in vitro and in vivo. J. Neuroinflammation 14, 84-84.
Wu, S.P., Tao, S., Liu, W.X., 2006. Particle size distributions of polycyclic aromatic hydrocarbons in rural and urban atmosphere of Tianjin, China. Chemosphere 62, 357–367.
Younan, D., Petkus, A.J., Widaman, K.F., Wang, X., Casanova, R., Espeland, M.A., Gatz, M., Henderson, V.W., Manson, J.E., Rapp, S.R., Sachs, B.C., Serre, M.L., Gaussoin, S.A., Barnard, R., Saldana, S., Vizuete, W., Beavers, D.P., Salinas, J.A., Chui, H.C., Resnick, S.M., Shumaker, S.A., Chen, J.-C., 2019. Particulate matter and episodic memory decline mediated by early neuroanatomic biomarkers of Alzheimer's disease. Brain 143, 289–302.
Yue, W., Tong, L., Liu, X., Weng, X., Chen, X., Wang, D., Dudley, S.C., Weir, E.K., Ding, W., Lu, Z., Xu, Y., Chen, Y., 2019. 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 22, 101161.
Zanobetti, A., Franklin, M., Koutrakis, P., Schwartz, J., 2009. Fine particulate air pollution and its components in association with cause-specific emergency admissions. Environ. Health : a global access science source 8, 58-58.
Zhang, Q., Li, Q., Ma, J., Zhao, Y., 2018. PM2.5 impairs neurobehavior by oxidative stress and myelin sheaths injury of brain in the rat. Environ. Pollut. 242, 994–1001.
Zhang, Y., Tao, S., 2009. Global atmospheric emission inventory of polycyclic aromatic hydrocarbons (PAHs) for 2004. Atmos. Environ. 43, 812–819.
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. The Lancet Planetary Health 4, e15–e23.