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Arboricultural Journal

The International Journal of Urban Forestry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tarb20

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To cite this article: Patrick Mei , Vaishali Malik , Richard W. Harper & Juan M. Jiménez (2021): Air pollution, human health and the benefits of trees: a biomolecular and physiologic perspective, Arboricultural Journal, DOI: 10.1080/03071375.2020.1854995

To link to this article: https://doi.org/10.1080/03071375.2020.1854995

Published online: 28 Jan 2021.

ARBORICULTURAL JOURNAL, 2021
https://doi.org/10.1080/03071375.2020.1854995

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Research Article

Air pollution, human health and the benefits of trees: a biomolecular and physiologic perspective

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ABSTRACT

It is well accepted that particulate matter (PM) can affect human health detrimentally. Chronic and prolonged exposures to particulate matter with an aerodynamic diameter ranging between 2.5 and 10 microns (PM_{10}), 0.1 and 2.5 microns ($PM_{2.5}$) and less than 0.1 microns in size (UFPM), have been associated with cardiopulmonary diseases. PM is ubiquitously present in urban settings, while primarily absent in forest environments primarily due to the direct interception of airborne pollution particles by trees. Both short- and long-term exposure to trees in forested environments is associated with lower blood pressure and inflammation, as well as enhanced immune function. Additionally, exposure to volatile organic compounds (VOCs) actively released by trees is associated with improved health through enhanced natural killer cell activity, reduced inflammatory responses, and reduced psychological stress. This article presents the results of a literature review on the harmful health effects of air pollution in urban environments, and the potential of forested environments to promote health and disease prevention.

KEYWORDS

Cardiovascular Health; Forest Bathing; Green Spaces; PM; VOC

Introduction

According to the United Nations State of World Population Report, the year 2008 was the turning point when more humans lived in urban settings than rural environments. This shift has accelerated the need to understand the effects on human health due to living in urban environments in comparison to rural settings, which may be more forested. Forested environments contain relatively less particulate matter due to active reduction of ozone, $PM_{2.5}$, and PM_{10} levels by trees (Nowak, Hirabayashi, Bodine, & Greenfield, 2014). The number of cases of cardiovascular disease, inflammation, and psychological health problems is less frequent for individuals living in or near forest environments (Maas et al., 2009, ; Nowak et al., 2014; Nowak, Hirabayashi, Bodine, & Hoehn, 2013). Forest environments have also been associated with other health benefits ranging from changes in mood to feelings of well-being (Beute & de Kort, 2014; Oh et al., 2017; Stigsdotter, Corazon, Sidenius, Kristiansen, & Grahn, 2017). In contrast, allergic,

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auto-immune, inflammatory and infectious diseases are associated with air pollution, which is more prevalent in urbanised environments (Flies et al., 2019). Given the interconnectedness of physiological and psychological health, this article reviews studies that explore air quality, its effects on cardiopulmonary, immunological, neurological, and psychological human health in the urban environment, and also explores the functions that trees and forested settings may play in mitigating these impacts.

Methods

An initial literature search was conducted with the intention of identifying publications that offered significant insight into human physiological (i.e. cardiovascular, cerebrovascular, respiratory) and psychological health effects associated with exposure to trees and forests. Such publications included elements like various populations, sample sizes, and geographic locales, evidence-based practices, and measurable physiological and psychological effect parameters. These multiple studies expounded upon practical frameworks and methodologies for the preparation of experimentation in forest environments. Databases searched included PubMed Central, PubMed, NCBI, ScienceDirect, and journals in the fields of cardiovascular, nervous system, pulmonary system, and psychology (Table 1). Examination of bibliographies and reference lists from seminal researchers of cardiovascular, neurologic, pulmonary, and psychological conditions were also applied to the initial selection of publications. Keywords and Boolean operators AND/OR were used for each database during snowball searches. These terms were chosen from careful analyses of supporting literature.

Diseases and air pollution

Air pollution is one of the most pervasive health stressors in urban environments. It is unquestionably not a new problem, but the composition of air pollution has changed throughout the centuries. During the industrial revolution, coal was one of the main contributors to air pollution, but this changed as cities evolved and sources of pollutants expanded to include other types such as vehicular exhaust. Urban air pollution now primarily consists of diverse molecules, such as ground-level ozone, lead, carbon monoxide, sulphur dioxide, nitrogen dioxide, and particulate matter (PM), all of which have been classified as harmful pollutants (Brook et al., 2002; Burnett, Dales, Brook, Raizenne, & Krewski, 1997; Chen, Kuschner, Gokhale, & Shofer, 2007; Gojova et al., 2007; Gryparis et al., 2004). PM can float in the air for an extended period and can be easily inhaled due to their small sizes. PM pollution has been associated with adverse effects in respiratory and pulmonary functions directly linking health risks with particulate matter (Pope, 2002; Pope et al., 2004). Cardiovascular morbidity and mortality increases with prolonged exposure to PM (Pope et al., 2004; Tsao et al., 2014). Clinical data correlates low levels of PM with decreased blood pressure, serum cortisol levels, inflammatory cytokines, and sympathetic nervous activity (Kobayashi et al., 2017; Kuo, 2015; Li et al., 2011; Mao et al., 2017; Sung, Woo, Kim, Lim, & Chung, 2012; Tsao et al., 2014). Markers of neurodegenerative disease have also been observed to correlate with $PM_{2.5}$ exposure (Chen et al., 2015; Wilker et al., 2015). The broad harmful health effects of PM exposure were

Table 1. Health benefits associated with trees (selected articles).

Authors and Publication Date	Article	Results and Conclusions
Tsao T-M., Tsai M-J., Wang Y-N., Lin H-L., Wu C-F., et al. (2014)	*The Health Effects of a Forest Environment on Subclinical Cardiovascular Disease and Health-Related Quality of Life*	Individuals located in forest environments featured improved subclinical CVD's markers of carotid IMT.
Nowak D., Hirabayashi S., Bodine A., Greenfield E. (2014)	*Trees and forest effects on air quality and human health in the United States*	Urban trees remove substantial amounts of pollution (i.e. O_3 and PM), providing human health benefits.
Furuyashiki A., Tabuchi K., Norikoshi K., Kobayashi T., Oriyama S. (2019)	*A comparative study of the physiological and psychological effects of forest bathing (Shinrin-yoku) on working age people with and without depressive tendencies*	A day long forest bathing session lowered the blood pressure, heart rate, and improved profile of mood states emotional health metrics in subjects with depressive tendencies.
Mao G., Cao Y., Wang B., Wang S., Chen Z., et al. (2017)	*The Salutary Influence of Forest Bathing on Elderly Patients with Chronic Heart Failure*	Decreased level of inflammatory cytokines and improved antioxidant function observed in the forest group. Negative emotional mood state wall alleviated after forest bathing. A better air quality in the forest site was observed according to the detection of $PM_{2.5}$ and negative ions.
Li Q., Otsuka T., Kobayashi M., Wakayama Y., Inagaki H., et al. (2011)	*Acute effects of walking in forest environments on cardiovascular and metabolic parameters*	Habitual walking in forest environments may lower blood pressure by reducing sympathetic nerve activity and improve blood adiponectin and DHEA-S levels; may also have beneficial effects on blood NT-proBNP levels.
Li Q., Kobayashi M., Kumeda S., Ochiai T., Miura T., et al. (2016)	*Effects of Forest Bathing on Cardiovascular and Metabolic Parameters in Middle-Aged Males.*	Walking 2.6 km for 80 minutes significantly reduced pulse rate and significantly increased the score for vigour and decreased the scores for depression, fatigue, anxiety, and confusion. Urinary adrenaline after forest bathing also showed a slight decrease. Urinary dopamine after forest bathing was significantly lower than that after urban area walking, suggesting the relaxing effect of the forest bathing. Serum adiponectin after the forest bathing was significantly greater than that after urban area walking.
Ideno Y., Hayashi K., Abe Y., Ueda K., Iso H., Noda M., Lee S L., Suzuki S. (2017)	*Blood Pressure-Lowering Effect of Shinrin-yoku (Forest Bathing): A systematic review and meta-analysis.*	Systolic blood pressure of the forest environment was significantly lower than that of the non-forest environment. Additionally, diastolic blood pressure of the forest environment was significantly lower than that of the non-forest environment.
Barton J., Rogerson M. (2017)	*The Importance of Greenspace for Mental Health.*	Research indicates that potential mechanisms underpinning the positive relationship between greenspace and health are likely to include sensory-perceptual and immunological processes, air quality, physical activity, stress and social integration.

(*Continued*)

Table 1. (Continued).

Authors and Publication Date	Article	Results and Conclusions
Nowak D J., Hirabayashi S., Bodine A., Greenfield E. (2014)	*Trees and Forest Effects on Air Quality and Human Health in the United States*	Computer simulations with local environment data reveal that trees and forests in the conterminous US removes 17.4 million tonnes (t) of air pollution in 2010.
Wilker E., Preis S., Beiser A., Wolf P., Au R., Kloog I., Li W., Schwartz J., Koutrakis P., Decarli C., Seshadri S., Mittleman M. (2015)	*Long-Term Exposure to Fine Particulate Matter, Residential Proximity to Major Roads and Measures of Brain Structure*	Exposure to fine particulate matter associates with total brain white matter volume reduction and higher probability of brain infarcts.
Pope C., Burnett R., Thun M., Calle E., Krewski D., Ito K., Thurston G. (2004)	*Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution*	Fine particulate and sulphur oxide-related pollution increases the risk of cardiopulmonary morbidity and mortality.

highlighted in a 2016 World Health Organisation (WHO) report emphasising 4.6 million premature deaths due to ambient air pollution (World Health Organization, 2016).

Mechanisms of PM-induced responses

To understand the relationship between PM exposure and cardiovascular diseases, it is essential to consider the mechanisms and pathways involved in the disease. Although the inflammatory response pathway is commonly associated with a protective mechanism that cells employ as a defence against injury and infection, it can also play a detrimental role in some diseases, including cardiovascular disease. For example, in the most common cardiovascular disease, atherosclerosis, the pro-inflammatory phenotype in arteries can result in the growth of plaques in the arterial wall, leading to morbidity and mortality. In the presence of PM, the pro-inflammatory phenotype in arteries is further exacerbated, potentially aggravating atherosclerotic lesions (Figure 1). Air particulate matter of small size and diameter can enter the respiratory tract during inhalation. Once in the lungs, PM can cross the pulmonary epithelial-endothelial barrier into the bloodstream (Pope, 2002). In the bloodstream, PM can interact with endothelial cells, the innermost layer of blood vessels, and promote permeability, which in turn increases transport across endothelial cells into the wall of arteries – a distinctive characteristic of inflammation (Chuang, Chan, Su, Lee, & Tang, 2007; Gojova et al., 2007; Hirota et al., 2012). To determine if PM truly causes inflammation, multiple studies have measured the concentration of inflammation biomarkers in the blood of test subjects, such as C-reactive protein and inflammatory cytokines (Pope et al., 2004; Chuang et al., 2007; Yin et al., 2017). Unequivocally, inflammation biomarker concentration is markedly increased in the blood of subjects after exposure to air particulate matter, metal oxides, sulphates, and ozone (Brook et al., 2002; Gryparis et al., 2004; Gojova et al., 2007; Yin et al., 2017).

Respiratory diseases

Respiratory diseases affect the lungs potentially altering the capacity to breathe and exchange gases. Air enters the lungs and travels to the smallest branches where gases

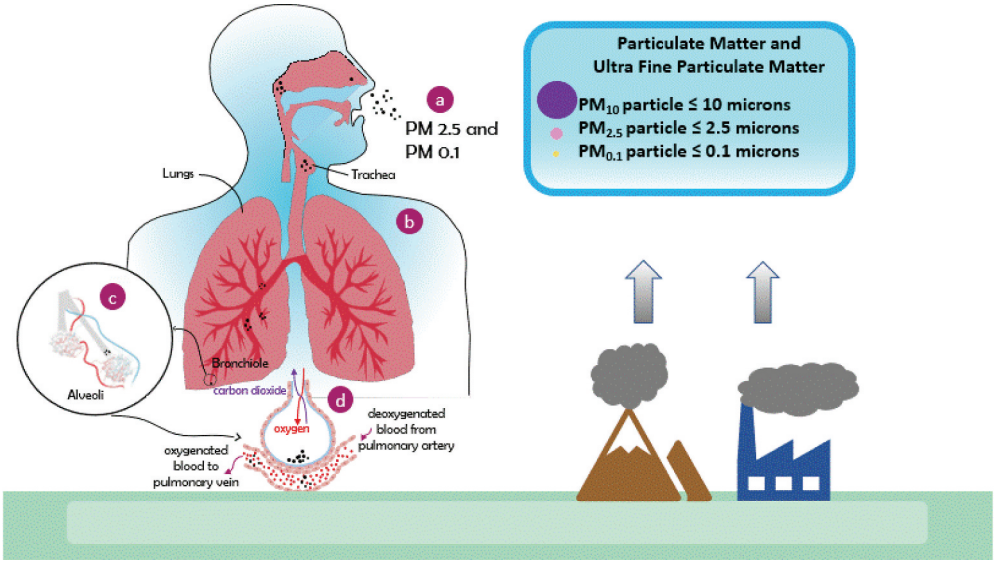

Figure 1. Particulate matter sources vary from a wide range of both human and natural origins, including industrial processes, transport usage and natural causes such as volcanic eruptions. (a) PM enters the body through the nasal passages and mouth. (b) These molecules travel down the trachea and into the bronchi. (c) PM travel from the bronchi into the alveoli. (d) Within the alveoli gas exchange occurs crossing the epithelial-endothelial cell interface and into the blood capillaries. Once in the blood, PM can travel throughout the circulatory system.

are exchanged at the epithelial-endothelial cell interface. Epithelial cells make up the inner layer of the lungs, while the endothelial cells compose the inner layer of blood vessels. Different respiratory diseases can affect gas exchange in the lungs increasing breathing difficulties. Of the different types of respiratory diseases, obstructive lung diseases, chronic respiratory diseases, respiratory tract infections, and cancers are strongly affected by PM (Karakatsani et al., 2012; Kelly & Fussell, 2011; Sax, Zu, & Goodman, 2013; Vineis et al., 2006). The impact of PM_{10} and nitrogen dioxide (NO_2) on human health was assessed in an Italian study using air pollution data from regional environmental agencies (Faustini et al., 2013). Increases in chronic obstructive pulmonary disease (COPD) related emergency hospitalisations were associated with increased exposure to PM_{10} and NO_2. These patients tended to be affected more severely due to lower respiratory tract infections (LRTI). A meta-analysis of more than one million COPD-related acute events linked COPD emergency department visits and hospital admissions with an increase in $PM_{2.5}$, NO_2, and sulphur dioxide (SO_2). To address the question if COPD patients suffer from PM-induced chronic inflammation, a 2-year observational cohort study of COPD patients was conducted (Gao et al., 2020). During regular follow-ups, blood serum levels of 20 cytokines and small secreted proteins released by cells were measured and correlated with the geocoded residential address of the participants to estimate the daily exposure to air pollutants. Increased systemic inflammation on COPD patients correlated with short-term exposure to air pollutants. Furthermore, forced vital capacity (FVC), a metric for lung function due to the total amount of air exhaled, was reduced in COPD patients after acute exposure to $PM_{2.5}$, NO_2, SO_2, and

carbon monoxide (CO). Prolonged exposure to PM may promote chronic inflammation and contribute to remodelling of pulmonary airways and decrease airflow in the lungs.

During the 1996 Summer Olympic Games in Atlanta, Georgia, USA, vehicular traffic decreased in the city of Atlanta resulting in decreases in peak daily ozone levels that strongly associated with significantly lower rates of childhood asthma (Friedman, 2001). In a separate study, asthmatic children in urban settings exposed to higher concentration of NO_2, sulphur dioxide, and $PM_{2.5}$ experienced significantly lower pulmonary function (O'Connor et al., 2008). A meta-analysis, focused on short-term air pollution exposure, found an association between PM_{10} and asthma episodes (Weinmayr, Romeo, De Sario, Weiland, & Forastiere, 2010). Although air pollutants are responsible for asthma exacerbation, they have also been suggested to cause new-onset asthma (Dong et al., 2011). Suggested mechanisms for asthma exacerbation due to air pollution are oxidative injuries in the pulmonary airways that promote inflammation, remodelling of the airways, and increased sensitisation (Guarnieri & Balmes, 2014). Chronic inflammation is characteristic of asthma patients accompanied by airway hyper-responsiveness and tissue remodelling of the airway structure (Murdoch & Lloyd, 2010). Given that the immune system of asthma patients reacts to non-pathogenic stimuli that can lead to chronic inflammation, air pollution is a risk factor for asthma patients (HOLGATE, 2008).

Fine particulate and sulphur oxide-related pollution has been linked to lung cancer (Pope, 2002). In a nine country European analysis of 17-study cohorts, geocoded air pollution showed a statistically significant association between increased risk for lung cancer and PM (Raaschou-Nielsen et al., 2013). Given the functions of the lungs and its physical interaction with the air and potentially accompanying air pollution, it is reasonable to expect an increased risk of lung cancer due to exposure to air pollution. However, the Cancer Prevention Study II demonstrated an association between exposure to air pollutants and increased risks of other cancer types as well (Pope, 2002). An analysis of more than 600,000 participants in the Cancer Prevention Study II showed significantly positive association between outdoor air pollution and kidney and colorectal cancers (Turner et al., 2017).

Arguably, air pollution plays an important role in the onset and exacerbation of respiratory diseases, including cancer.

Cardiovascular diseases

Atherosclerosis is one of the leading cardiovascular diseases worldwide and involves an active inflammatory response leading to blood vessel narrowing and restricted blood flow (Libby, Ridker, & Maseri, 2002). With increased plaque build-up inside the blood vessel wall, arteries are affected by arterial stiffening where the blood vessels thicken and are unable to constrict and dilate properly. Increased arterial stiffening can impose increased strain on the heart and lead to heart failure (Pandey et al., 2017). Atherosclerotic plaques can rupture and cause a fatal heart attack (Herrington, Lacey, Sherliker, Armitage, & Lewington, 2016). Initiation of atherosclerosis starts with the dysfunction of the endothelial cells that line the inner layer of blood vessels. High LDL cholesterol, diabetes, high blood pressure, sex hormone imbalance, ageing, inflammation, infectious agents, disturbed blood flow and environmental toxins, such as air

pollutants, have been identified as risk factors for endothelial cell dysfunction and initiation of atherosclerosis (Gimbrone & García-Cardeña, 2016).

A population study in 2003 suggested that, out of all data obtained from a Cancer Prevention Study (CPS) from the American Cancer Society (ACS), 45% of deaths had been attributable to cardiovascular disease. The empirical data analysed revealed specific relationships between fine air particulate matter and accelerated atherosclerosis, pulmonary and systemic inflammation, and altered cardiac autonomic function (Gojova et al., 2007; Pope, 2002; Pope et al., 2004). The effects of long-term exposure to air particulate matter and sulphur dioxide-related pollution, as well as ambient air pollution, directly correlated with symptoms of poor cardiovascular health and exacerbation of existing cardiovascular or cardiopulmonary diseases (Burnett et al., 1997; Chen et al., 2007; Künzli et al., 2010; Pope, 2002; Pope et al., 2004). Tsao et al. (2014) noted that short-term exposure to PM_{10}, $PM_{2.5}$, and nitric oxides contribute to an increased risk of cardiovascular diseases. Many studies converge on the harmful effects of air pollutants on cardiovascular and cardiopulmonary health (Block & Calderón-Garcidueñas, 2009; L. Calderón-Garcidueñas et al., 2008; Chuang et al., 2007; Lawal, 2017; Li, Guan, Tao, Wang, & He, 2018; Pope et al., 2004; Suwa et al., 2002; Tsao et al., 2014).

Exposure to particulate matter increases the concentration of C-reactive protein and other inflammatory markers circulating in the blood (Chuang et al., 2007; Yin et al., 2017 ; Pope et al., 2004). At the biochemical and molecular level, particulate matter induces various responses such as programmed cell death of the vascular endothelial cells, and the increase of inflammatory cytokines, causing inflammation in the endothelial cells (Hirota et al., 2012; Tsao et al., 2014; Yin et al., 2017). *In vivo* experiments have shown that inhalation of nanoparticles leads to impaired endothelial cell-dependent vasodilation in cardiac vessels (LeBlanc et al., 2009, 2010). In healthy volunteers devoid of cardiovascular risk factors, endothelial cell dysfunction was correlated with exposition to ambient air pollution in a large artery and an exaggerated dilatory response in small arteries (Briet et al., 2007). Long-term exposure to ambient air pollution was linked to increased inflammatory markers in the blood of a multi-ethnic cohort (Hajat et al., 2015). Increased inflammatory markers in the blood increase the risk of endothelial dysfunction and atherosclerosis (Gimbrone & García-Cardeña, 2016). The effects of air pollution extend to epigenetic modification of cellular DNA where exposure to increased NO_2, PM_{10}, $PM_{2.5}$, and O_3 decreased global DNA methylation in non-smoking adults (De Prins et al., 2013).

Air pollution found in urbanised areas promotes inflammation, which contributes to cardiovascular disease, including atherosclerosis.

Cerebrovascular disease, cognitive impairment, and mental illness

It is well known that long-term exposure to air PM correlates with cerebrovascular disease and cognitive impairment (Ljungman & Mittleman, 2014; Power et al., 2011; Weuve, 2012). More recently, it has been shown that exposure to $PM_{2.5}$ is associated with a smaller total cerebral brain volume, a common feature of age-associated brain atrophy (Wilker et al., 2015). In a separate study focusing on women, white matter loss in older women was associated with $PM_{2.5}$ exposure (Chen et al., 2015). White matter changes are linked to decreased memory, processing speed, and executive function

(Gunning-Dixon & Raz, 2000). Air pollution has also been associated with other neurodegenerative diseases. An 11 year-long correlative study of 9.8 million patients in 50 north-eastern U.S. cities observed significant association between long-term $PM_{2.5}$ exposure and increased risk for dementia, Alzheimer's disease, and Parkinson's disease (Kioumourtzoglou et al., 2016). In addition to long-term exposure to fine particles ($PM_{2.5}$), a Taiwanese study suggested that long-term exposure to ozone (O_3), created when by-products of combustion and sunlight interact, is associated with increased risk of Alzheimer's disease (Jung, Lin, & Hwang, 2015).

Given that brain morphometric changes are associated with long-term exposure to air pollution, it is expected that air pollution causes phenotypic changes at the cellular level. *In vivo* experiments have demonstrated that exposure to particles, ozone, or combinations of particles and ozone changed the mRNA synthesis levels of genes involved in vasoregulation in the cerebral hemisphere and the pituitary gland (Thomson, Kumarathasan, Calderón-Garcidueñas, & Vincent, 2007). The olfactory and respiratory nasal mucosae, olfactory bulb, and cortical and subcortical structures from mongrel dogs living in Mexican cities with differing levels of air pollution were evaluated to elucidate the effects of air pollutants on the upper and lower respiratory tract (Calderón-Garcidueñas et al., 2002). Changes in the inflammation-related genes nuclear neuronal NF-kappaB and iNOS were observed in cortical endothelial cells. Further detrimental changes due to air pollution included remodelling of the blood-brain barrier, degeneration of cortical neurons, apoptotic glial white matter cells, deposition of apolipoprotein E (apoE)-positive lipid droplets in smooth muscle cells and pericytes, nonneuritic plaques, and neurofibrillary tangles. In dogs exposed to air pollution, a similar study showed via immunohistochemistry increased nuclear neuronal NFkappaB p65, a critical step in inflammation (Calderón-Garcidueñas et al., 2003). Further observed changes were observed in endothelial, glial, and neuronal iNOS, in addition to endothelial and glial cyclooxygenase-2 (COX2). ApoE was observed in neuronal, glial, and vascular cells, which has been suggested as a risk factor of Alzheimer's disease. Amyloid precursor protein and beta-amyloid (1–42) in neurons, diffuse plaques, and in subarachnoid blood vessels were also observed, even in dogs as young as 11 months old. Occasionally experimental animal results do not translate to human health. To address this concern, brain autopsy samples from lifelong residents of cities with varying pollution levels were assessed for protein synthesis levels of the inflammatory mediator COX2 and accumulation of the 42-amino acid form of beta-amyloid (Aβ 42), which causes neuronal dysfunction (Calderón-Garcidueñas et al., 2004). In contrast to residents of lower air pollution cities, residents of cities with higher air pollution burden showed significantly higher COX2 accumulation in the frontal cortex and hippocampus. Similarly, higher air pollution correlated with greater neuronal and astrocytic accumulation of the 42-amino acid form of beta-amyloid. The findings suggest an association of long-term exposure to air pollution with brain inflammation and Aβ 42 accumulation in neural tissue, a risk factor for Alzheimer's disease.

The previously highlighted studies demonstrate the impact of PM on inflammation of the central nervous system. Consequently, effects to the central nervous system (CNS) are expected to affect mental health. Accumulating evidence of human and animal studies point to the potential role of PM-induced CNS inflammation in increased risk for

depressed mood, anxiety disorders, bipolar disorder, and other mental health problems (Barron, Hafizi, Andreazza, & Mizrahi, 2017). Although harder to assess, different studies have attempted to elucidate the role of PM on mental illness. In a Northern California study, 144 adolescents participated in a modified Trier Social Stress Test with heart rate and skin conductance as the physiologic metrics of stress (Miller, Gillette, Manczak, Kircanski, & Gotlib, 2019). Greater levels of stress were associated with adolescents residing in higher $PM_{2.5}$ concentration neighbourhoods. A nationally representative panel data from the USA's Environmental Protection Agency Air Quality System was used to determine if a relationship between psychological distress and air pollution existed. When controlling for demographic, socioeconomic, and health-related covariates, higher concentrations of $PM_{2.5}$ positively associated with psychological distress (Sass et al., 2017). A recent meta-analysis determined that long-term $PM_{2.5}$ exposure associates with depression, and a potential association with short-term PM_{10} exposure and suicide (Braithwaite, Zhang, Kirkbride, Osborn, & Hayes, 2019).

Particulate matter reduction strategies for health improvement

There has been an increase in the use of face masks due to increased awareness of the negative impact of particulate matter on human health. A study in 2012 assessed cardiovascular health metric changes in coronary artery disease patients due to air pollution exposure reduction through the use of a face mask (Langrish et al., 2012). The study reported an improvement in heart rate variability and function, as well as reduction in systolic blood pressure. It has been further postulated that individuals with a history of chronic air pollution exposure and those with pre-existing cardiovascular diseases can benefit from reduced exposure resulting in an overall improvement in health (Langrish et al., 2012). A study performed on the effectiveness of N95 face masks in China determined that 48–75% concentration of ambient air particles between 5.6 and 560 nm in diameter were prevented from entering the airways (Guan, Hu, Han, & Zhu, 2018). Although the N95 face masks partially reduced acute particle-associated airway inflammation, it did little in reducing oxidative stress and endothelial dysfunction. There is a greater need to determine long-term significance of these tests, since filtration efficiency of masks is strongly dependent on proper usage and proper face seal (Qian, Willeke, Grinshpun, Donnelly, & Coffey, 1998).

Trees: particulate matter sinks and beneficial volatile organic compounds sources

Forested environments have lower air PM concentration than urban settings since trees act as biological filters that remove and intercept air particles. A direct result of this biological filtering is lower levels of gaseous pollutants, such as NO_2, SO_2, $PM_{2.5}$, and ozone (Nowak et al., 2013; Yang, McBride, Zhou, & Sun, 2005). Lowering of gaseous pollutants is not limited to forests, but also relevant in inner cities where forested patches have demonstrated significant removal of gaseous pollutants (Cavanagh, Zawar-Reza, & Wilson, 2009; Nowak et al., 2014). Although it is known that gaseous pollutants such as SO_2, NO_2, and ozone are absorbed by the tree leaf stomata, it is not trivial to quantify pollution removal by trees. In one study, different analyses were conducted to try to determine the magnitude to which trees affect air quality in the United States of

America. The first analysis focused on determining tree cover and leaf area index using data from the National Land Cover Database (NLCD). A separate analysis focused on health incidence effects and monetary value of NO_2, SO_2, ozone, and $PM_{2.5}$ as estimated from the USA Environmental Protection Agency BenMAP programme. Lastly, the hourly pollution removal by trees and the change in pollution concentration were calculated to determine the effect of trees on air quality. A positive correlation between the amount of tree cover and the removal of air pollutants was revealed. The trees substantially improved air quality because of the significant removal of ozone and $PM_{2.5}$ (Nowak et al., 2014). Similarly, another study conducted in Beijing, China involved the analysis of satellite images and field surveys to determine the influence of an urban forest patch on air quality. Considering the high concentration of air pollution within the inner city, 2.4 million trees had removed 1261.4 tons of pollutants, namely PM_{10}, substantially improving air quality (Yang et al., 2005). However, not all trees have the same capacity to filter the air, as shown by a recent analysis to determine optimal foliar traits for effective $PM_{2.5}$ capture. Trees like conifers, with acicular needle shapes were more efficient at $PM_{2.5}$ capture than broadleaved species (L. Chen, Liu, Zhang, Zou, & Zhang, 2017). This is an important consideration when PM removal is the goal.

Trees act as biological filters of pollutants through the interception of particles and gaseous absorption, resulting in reduced particulate matter and improved air quality (Q. Li et al., 2008; Nowak et al., 2013; Yang et al., 2005). However, it is not just the absence of PM in forest environments that may be playing a role in health benefits, but also what trees may be releasing. The combined release of phytoncides, a class of volatile organic compounds (VOCs) that act as microbicides, from trees have been suggested to play a potential role in improving the air quality and enhancing bodily immune function by increasing natural killer cell function and activity (Li et al., 2009). These organic compounds may also be involved in an elevated positive emotional state and increased parasympathetic nervous activity (Li et al., 2011).

Forested environments lower biomarkers of cardiovascular disease

Forest bathing, the practice of spending intentional time in natural-wooded settings for the affiliated health benefits has been suggested as a treatment for diseases (Park, Tsunetsugu, Kasetani, Kagawa, & Miyazaki, 2010). The motivation for forest bathing is based on the theory of biophilia that attempts to describe the human appeal for water, grass (savannah), trees, and other natural factors, as being rooted in a longstanding relationship of humans and their surrounding environment (Wilson, 1992). Forest bathing studies have explored the relationship of spending time exposed to forested environments surrounded by vegetation and changes in the levels of cardiovascular disease markers in the blood serum of participants. Imbalanced levels of these biomarkers may increase the risk of cardiovascular diseases. One such study asked participants to exercise in an urban environment in the morning and afternoon for 2 hours, and repeated the same routine exercise in a forest park a week later (Li et al., 2011). Blood was drawn 24 hours before and after each exercise day. The results showed that many well-known cardiovascular disease biomarkers, such as triglycerides, total cholesterol, LDL, HDL, RPL and hs-CRP, were unchanged. However, two protective biomarkers, adiponectin and DHEAS-S, had increased in the subjects after exercising in the forest

park, while remaining unchanged after exercise in the urban environment. Low levels of both adiponectin and DHEAS-S are associated with higher risk of developing cardiovascular diseases. A significant decrease in the detrimental serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) was also observed after walking in the forest park. The increase in blood serum levels of adiponectin and DHEAS-S and decrease of NT-proBNP, suggested that not just exercising, but exercising in a forest park can have superior benefits relative to exercising in an urban setting (Li et al., 2011). Although promising, this study focused only on healthy subjects and not on the elderly and infirmed. A separate study addressed this dearth by assessing if forest bathing can be beneficial for elderly patients with chronic heart failure (Mao et al., 2017). Study subjects were separated into two groups that visited either a forested or urbanised environment for four days. Subjects visiting the forested environment experienced significant reduction in brain natriuretic peptide (BNP), a congestive heart failure biomarker, in comparison to their initial levels and the initial and final levels of the urban group. Blood serum levels of other cardiovascular disease biomarkers, including endothelin-1 (ET-1), and constituents of the renin-angiotensin system (RAS), including renin, angiotensinogen (AGT), angiotensin II (ANGII), and ANGII receptor type 1 or 2 (AT1 or AT2) were lower than those of the urban group. Similarly, assessment of the profile of mood states (POMS) showed improvements in emotional mood states after forest bathing. Forest bathing has also shown improvements in the heart rate of both men and women alike (Ochiai et al., 2015; Tsunetsugu et al., 2013).

Forested areas lower blood pressure

Blood pressure is an important metric in cardiovascular diseases, and potential effects of forest environments on blood pressure regulation are of much interest. One study seeking to elucidate a potential relationship between exposure to forested areas and blood pressure enrolled subjects to exercise in a city environment and a week later in a forest park. On both trips, the subjects walked for 2 hours in the morning and afternoon for a total distance of about 6 km. Results found that blood pressure was significantly lower after the forest park visit than after the walk in an urban setting (Li et al., 2011). Other studies have found similar blood pressure lowering results and improvements in other health metrics by forest bathing. This suggests that although exercise itself can lower blood pressure, exercise in a forest environment can have a greater blood pressure lowering effect (Moreira, Cruz, Diniz, Albuquerque, & Carvalho, 2013; Lee & Lee, 2014; Li et al., 2016a; Ideno et al., 2017; Lanki et al., 2017).

Volatile Organic Compounds Secreted by Trees Boost the Human Immune System, Lower Stress Hormones, and Combat Inflammation

Forest environments also influence the immune system. Immune response has been explored by focusing on natural killer (NK) cells, which are lymphocytes that target viral-infected cells and tumours. A 2009 study looked at the immune activity of NK cells from randomly selected subjects that visited a forest for 3 days and compared NK activity from the same subjects on workdays and tourist excursions to an urban environment. Only the forest bathing trip increased NK activity (Li et al., 2009). This and other studies

prompted inquiries into what molecules in a forest environment may be boosting the immune system (Q. Li et al., 2008; Li, 2010). One subset of molecules that has become of interest are volatile organic compounds (VOCs) released by trees. It has been long known that trees of many species emit phytoncides, allelochemic VOCs that protect the trees against microbial, fungal, and insectile threats (Li et al., 2009). Could these VOCs be responsible for the increase in NK cellular observed in other studies? To address this question one study placed 12 healthy male subjects in a hotel room with heavy concentrations of vaporised Japanese cedar (*Cryptomeria japonica*) and Hinoki cypress (*Chamaecyparis obtusa*) for three consecutive nights. Blood and urinary samples were monitored for a variety of immune system function markers including white blood cell counts, natural killer cell activity, perforin levels, granzyme A levels, granulysin levels, and adrenaline and noradrenaline concentrations. The study showed that oil extracts from the Japanese cedar and Hinoki cypress influenced natural killer cell activity and its proliferation, as well as influenced the intracellular perforin levels, granzyme A levels, and granulysin levels within NK cells (Li et al., 2009). These effects are all desirable immune system traits.

VOCs, such as α-pinene, d-limonene, and oils derived from various species of trees not only have been shown to enhance natural killer cell activity, but also to reduce stress via blood serum cortisol level reductions (Li et al., 2008). Cortisol is a stress hormone released by the body under stressful conditions and increases blood pressure. Inhalation and exposure to pine (*Pinus* spp.) oil and cypress (*Cupressaceae spp*.) oil phytoncides reduces serum cortisol levels and consequently blood pressure (Nam & Uhm, 2008). VOCs also decrease adrenaline and noradrenaline levels, hormones involved in psychological distress (Calfapietra et al., 2013; Nam & Uhm, 2008). Decreased adrenaline and noradrenaline levels may suggest that phytoncides inhibit stress hormones, thereby potentially reducing the stress experienced by the individuals.

Studies that elucidated the effects of phytoncide derivatives on immunity found an increase in intracellular perforin levels, granzyme A levels, and granulysin levels (Li et al., 2009). However, the biochemical mechanisms by which VOCs secreted by trees affect the immune system are not completely understood. Recently, insights into the interaction of VOCs and the inflammation biochemical pathway have been uncovered. VOCs induce an anti-inflammatory response and analgesic effect through the inhibition of inflammatory proteins and overexpression of cyclooxygenase-2 (COX-2), an enzyme known for inducing pain relief through the production of prostanoids (Li et al., 2016). Though this category of phytoncides exhibits a biochemical mechanism for anti-inflammation, other phytoncides and VOCs may exhibit an entirely different mechanism.

Concentrations of phytoncides in urban environments are significantly lower when compared to forest environments positing why natural killer cell activity increases and stress hormones decrease in forests (Li et al., 2008). Phytoncides present a natural method of improving human immunity and mental health. With their essential roles in immunological and inflammatory responses, phytoncides and other VOCs may present a viable approach in reducing the harmful effects felt by air particulate matter. Further research and evidence are needed for a definitive conclusion on the clinical implications of VOCs secreted by trees.

Psychological health and forested environments

Forested environments may prove potentially beneficial to the mental health of individuals. The importance of nature and experiences around greenery and the natural world continues to be recognised with increasing importance, by a medical sector that has traditionally placed more of a curative, bio-pathological emphasis on human health (van den Bosch, 2017). Visual perception and close proximity to these spaces have been correlated with reduced levels of stress, thereby reducing the risks of developing mental health illnesses and improving well-being (Dolling, Nilsson, & Lundell, 2017; Svendsen, Northridge, & Metcalf, 2012 ; Wang, Rodiek, Wu, Chen, & Li, 2016). Associations with nature, for example individuals viewing natural sceneries and selections can more effectively reduce stress when compared to individuals observing scenes from the built environment (Dadvand et al., 2016; Kuo, 2015). Although it may be advisable to integrate green spaces into urban infrastructure to increase exposure to more naturalised environments and potentially reduce stress, assessing the positive effects of spending time in forest environments to justify costs may be nontrivial. Traditionally, mental health assessments after exposure to forested environments have relied on subjective self-reporting questionnaires. In recent years, a greater emphasis has been placed on coupling objective measurements of biomarkers that can serve as proxies for stress levels with subjective self-reporting psychological questionnaires with the goal of obtaining more impartial assessments. In a study by Lee, Park, Tsunetsugu, Kagawa, and Miyazaki (2009) 12 subjects were randomly selected to visit an urban or forested environment (Lee et al., 2009). Physiological and psychological data were collected four times a day for each subject. Subjects in the forest environment experienced significantly lower salivary cortisol concentration, blood pressure and pulse rate, all proxies for stress level measurements. The psychological results of the urban subjects mirrored their physiological outcomes showing decreased positive emotions. Other studies with relatively larger samples have shown similar trends where subjects exposed to urban settings experience physiological changes associated with increased stress levels, such as higher salivary cortisol concentration, blood pressure, and pulse rate along with more negative self-reported emotions (J. Lee et al., 2011; Tsunetsugu et al., 2013; Tyrväinen et al., 2014; Ward Thompson et al., 2012). Of note, these measurements correspond to acute exposure in a specific environment. If the results hold for chronic exposures, then it is likely that city dwellers experience prolonged increased stress levels, which are a major factor not only in physiological symptoms such as chronic fatigue and elevated stress hormones, but also various psychological consequences such as mental exhaustion and stress-induced mental illnesses (Dolling et al., 2017). In addition, urban dwellers are further exposed to physical environmental stressors commonly found in cities such as pollution, noise, and grey infrastructure, which may further contribute to increased stress levels and negative mental health effects (Galea, Uddin, & Koenen, 2011; Hartig et al., 2011; Park et al., 2011; Svendsen, Northridge, & Metcalf, 2012 ; Tyrväinen et al., 2014; Wang et al., 2016). These observations may partially explain the higher rates of major mental illnesses in urban environments where individuals are more likely to suffer from PTSD, distress, paranoia, schizophrenia, and depression (Galea et al., 2011). There is also increasing awareness that an overarching nature-deficit may be contributing to the growing numbers of youth struggling with conditions like attention

deficit hyperactivity (ADHD) (van den Bosch, 2017). Increasingly, medical treatment strategies include reconnecting youth with nature, supported by a growing body of literature that reinforces the relationship between mental cognitive health and exposure to green spaces (Amoly et al., 2014; Dadvand et al., 2016).

Efforts have been made to introduce green spaces as a part of urban infrastructure. It is becoming more common for cities to incorporate green spaces through parks and gardens to improve aesthetics and quality of life. These efforts have been propelled by studies that suggest that people's visual perception and closer proximity to nature and green spaces is associated with reduced stress levels (Dolling et al., 2017; Svendsen, Northridge, & Metcalf, 2012). Although the mechanisms remain elusive as to how and why green spaces may promote mental health benefits in humans, correlative studies have suggested that green spaces in urban environments promote improved mental health and well-being (Barton & Rogerson, 2017; Kuo, 2015). The restorative effects vary with location and amount of natural green settings. However, even exposure to a modest-sized urban park, has shown to correlate with improved psychological and emotional well-being (Larson, Jennings, & Cloutier, 2016; Svendsen, Northridge, & Metcalf, 2012 ; Wang et al., 2016; White, Pahl, Ashbullby, Herbert, & Depledge, 2013). As a result, suggestions have been made to study environmental biodiversity, air quality, sensory perception, and social community in order to elucidate the underlying mechanisms that benefit mental health and well-being (Barton & Rogerson, 2017; Svendsen, Northridge, & Metcalf, 2012).

Does length of exposure to forested environments matter?

Whether it is short-term or long-term exposure, particulate air pollution remains a risk factor for a variety of diseases. Long-term exposure to air particulate matter pollution has been suggested as a health risk factor by invoking various physiological responses such as inflammatory lung injury, elevated blood plasma viscosity, endothelial dysfunction, and myocardial infarction (Calderón-Garcidueñas et al., 2008; Pope et al., 2004). Ample evidence exists associating cardiovascular health with air quality, amongst other diseases (Pope et al., 2004).

A recent short-term exposure study assessed the risk of cardiovascular diseases on 114 urban and 107 forest workers by collecting data in relation to blood pressure, pulse rates, subjective Health-Related Quality of Life (HRQOL), as well as maximum intima-media thickness (IMT) of the carotid artery (Tsao et al., 2014). IMT is an important metric as it is an indicator of future progression of atherosclerosis and other cardiovascular diseases (Kablak-Ziembicka, 2004; Su, Hwang, Shen, & Chan, 2015). From this study, PM_{10}, $PM_{2.5}$, and nitric oxide were noted as contributing factors to cardiovascular diseases. The subjects exposed to the forested environments demonstrated superior health as evidenced by lower blood pressure, higher parasympathetic nervous activity and lower IMT (Tsao et al., 2014). The forest workers are exposed to a natural environment for extended periods raising the question if time exposure plays a role. In a separate study, individuals spending as little as 2 hours in forested environments demonstrated lower blood pressure and lower blood levels of Nt-proBNP and BNP, cardiac biomarkers associated with heart failure (Li et al., 2011). Additional data also indicated an increase in levels of serum adiponectin and DHEA-S (Li et al., 2011).

Chronic heart failure patients benefited from lower inflammatory markers, such as IL-6 TNF- α and C-reactive protein, after a four-day exposure to a forested environment (Mao et al., 2017). These data suggest that relatively short exposures to forested environments can decrease risk factors for heart disease, but can short exposures to forested environments improve mental health? Decades of research have suggested an interconnectedness between heart disease and mental illness (De Hert, Detraux, & Vancampfort, 2018). It could be expected that decrease in heart disease risk factors could improve mental health. A study including subjects with depressive tendencies demonstrated that after a day-long session of forest bathing, subjects with depressive tendencies demonstrated significantly greater improvements in metrics of depression in comparison to control subjects (Furuyashiki, Tabuchi, Norikoshi, Kobayashi, & Oriyama, 2019). Furthermore, all participants showed significant reduction in blood pressure and pulse rate, which are metrics of not only mental illness, but also of heart disease.

It can be reasonably expected that relatively short exposures to less air pollutants, namely $PM_{2.5}$ and PM_{10}, concomitant with forested environments may improve human overall health.

Conclusion

The continuing mass migration of humans to urban environments has highlighted the importance of understanding air quality and increased risk for diseases. Various risks in human health and well-being have been associated with this change in environment. Humans living in urban industrial environments are frequently exposed to PM_{10}, $PM_{2.5}$, and other air pollutants that induce inflammatory responses. Several physiological health risks have been correlated with this increased exposure, including cardiovascular and pulmonary diseases. Those already suffering from these diseases may even be at more risk with increased exposure to particulate matter. In contrast, forested environments can promote superior health outcomes due to the improved air quality and biological role of trees. Studies which compare the health outcomes of both environments indicate that forested environments provide more health benefits by releasing VOCs that boost the immune system, lower stress hormones, and reduce inflammation. Forested environments also improve well-being and mental health by reducing stress, promoting a positive emotional state, and eliciting feelings of well-being. Based on these findings, forests may provide a potential source of therapy in physiological and mental health for humans. From the studies considered for this review, it can be concluded that the influence of trees on the environment is of great impact and implementing green spaces such as parks or green indoor environments may positively influence urban human health.

Acknowledgments

We thank Dr Melissa D. Sánchez for constructive criticism.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by NSF grant CAREER CMMI1842308 (to J.M. Jiménez) and the USDA National Institute of Food and Agriculture – McIntire Stennis Project #34, Accession #1014171.

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