Association Between Access to Restorative Natural Environments and Decreased Chronic Inflammation

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Abstract: The efficiency of modern urban life is accompanied by many adverse health outcomes. Human biological responses to modernization depend on the adaptive mechanisms that developed in natural environments. This literature synthesis gathers evidence in support of the claim that exposure to nature increases relaxation and reduces negative rumination and chronic stress, and thereby improves immune health.

I provide an overview of the mechanisms through which exposure to nature impacts physiological and psychological functioning. Nature interventions improve cognitive function and decrease the risk of mental disorders and diseases through the feelings of awe and increased positive mood. Changes in mental health and well-being are attributed to the positive distraction away from oneself through nature, which uplift mood and reduce rumination. Stress reduction has positive effects on mental and physical fatigue, regulating the HPA axis and decreasing inflammation. Reduction of psychological stress and reinforcement of the mind-heart connection through exposure to nature restores immune health, affecting epigenetic patterns and microbiome eubiosis. Institutions can provide restorative natural environments and access to adequate green space through sustainable urban design methods, climate control and regulation, and socioeconomic equality.

1. Introduction

Dramatic alterations to human lifestyle and natural ecosystems have taken place as a consequence of urbanization, industrialization, and associated degradation of the natural environment (Claesson et al., 2012; De Vries et al., 2003; Maller et al., 2006; Rook et al., 2013; Ulrich et al., 1991). Land and water contamination with hazardous chemicals, climate change with more extreme and unpredictable weather, natural disasters, and the shift to high-density urban living has negatively impacted human health (Andersen et al., 2021; McMichael et al., 2008; Thoma et al., 2021). Increases in adjusted death rates and higher mortality rates are seen in areas with environmental degradation, such as deforestation, soil erosion, depletion of the ozone layer, water pollution, and environmental toxins (Andersen et al., 2021; Brunet et al., 2002 Myers, 2017; Song et al., 2016).

The modernization-associated environmental changes mentioned above are linked to a significant rise in preventable and non-communicable diseases (Frumkin et al., 2019), indicating a complex relationship between the environment and human health. These chronic diseases have been associated to the combination of a sedentary lifestyle, an unbalanced diet, and chronic psychological stress (Adams et al., 2016; Ammar et al., 2020; Duncan et al., 2020; Mattioli et al., 2020). The trends are even more pronounced in marginalized populations with less access to a balanced diet and safe spaces for recreational activities (Ammar et al., 2020; Duncan et al., 2020; Mattioli et al., 2020; Pahwa et al., 202; Sallis et al., 2021; Suzuki et al., 2020). There has been an exacerbation of chronic stressors due to the common components of everyday life (Gazzaniga and Heatherton, 2003). However, it is important to acknowledge that stress is not a modernization induced issues, as it has been a universal problem throughout human history due to past environmental and lifestyle difficulties (Hutmacher, 2021).

A growing body of evidence suggests that various forms of nature exposure can provide relief from negative psychological effects such as cognitive functioning, functioning of awareness, feelings, or motivations and associated physiological effects including blood pressure, heart rate, and stress hormones (Andersen et al., 2021; Myers, 2017; Song, et al., 2016; Segerstrom and Miller, 2006; Thoma et al., 2020). More broadly, recent work has explored the links between chronic psychological stress and mental and physical health problems through induction of immune system dysfunction and chronic inflammation (Marshall et al., 2002; O'Malley 2020; Pahwa et al., 2021; Turner et al., 2020).

This thesis reviews and synthesizes literature on the relationship between health outcomes and exposure to nature. I aim to emphasize information gaps in order to facilitate future research. I document evidence in support of the hypotheses that:

(i) Access to restorative natural environments is associated with decreased chronic inflammation. Human responses to natural environments act as mediators between nature exposure and the resolution of inflammation.

(ii) Nature exposure provides several integrated mechanisms that link stress to the onset of chronic inflammation, and conversely, link relaxation to prevention of chronic inflammation.

Additionally, I discuss the role of decreased rumination and mood elevation suggested by recent work (Bratman et al., 2015; Lopes et al., 2020; Nolen-Hoeskema et al., 2008) in the context of restoration of balanced stress and immune responses. I argue that both direct and indirect effects of nature exposure can be identified as providing inputs into key regulators of stress and immune response. Finally, I address the effects of restorative environments on human health in view of the fact that less than 0.01% of human history has been spent in urbanized environments (Brunet et al., 2002; Dye, 2008; Song et al., 2016).

2. Background

The World Health Organization (WHO) has identified industrialized countries as prime sites for health issues associated with chronic psychological stress (World Health Organization, 2006). Such chronic stress has been suggested to be a common risk factor for 75% of preventable diseases and 90% of non-communicable diseases (Cohen et al., 2007, Shuda et al., 2020). In general, human immune responses include both protective and pathological responses (Dhabhar et al., 1995, 1997, 2009; 2014; Pahwa et al., 2018). The protective immune response is fundamental to survival (Dhabhar, 1997, 2009; Goldstein et al., 2002) and is triggered by short-term acute stress (Dhabhar et al., 1997; 2009; Rook 2013). Harmful immune responses occur under chronic, long-lasting stress (Irwin et al., 1990; McEwen, 1998; Dhabhar, 2009).

Acute psychological stress suppresses the parasympathetic nervous system (Andersen et al., 2021; Song et al., 2016) that fosters resting (Lee et al., 2012; McMahan and Estes, 2015), digestion, and repair/maintenance functions (Karin et al., 2020), presumably to focus all available resources on the fight-or-flight response. Acute stress activates the stress system, i.e., the hypothalamus-pituitary-adrenal (HPA) axis (Dhabhar and McEwen, 1996; Dhabhar, 2009), producing stress hormones (Karin et al., 2020) and suppressing the immune system (Segerstrom and Miller, 2006). These effects are part of the broader stimulation of the sympathetic autonomic nervous system by stress (McClelland et al., 1980), which coordinates the alarm reaction known as fight-or-flight response (Dhabhar and McEwen, 1997; Dhabhar, 2009; Maller et al., 2006; Stegerstrom and Miller, 2006) in which heart rate increases, blood flow to the muscles and brain increases, and blood flow to the intestines and other non-essential organs decreases (Dhabhar and McEwen, 1997; Dhabhar and McEwen, 2001; Stoffel et al., 2020).

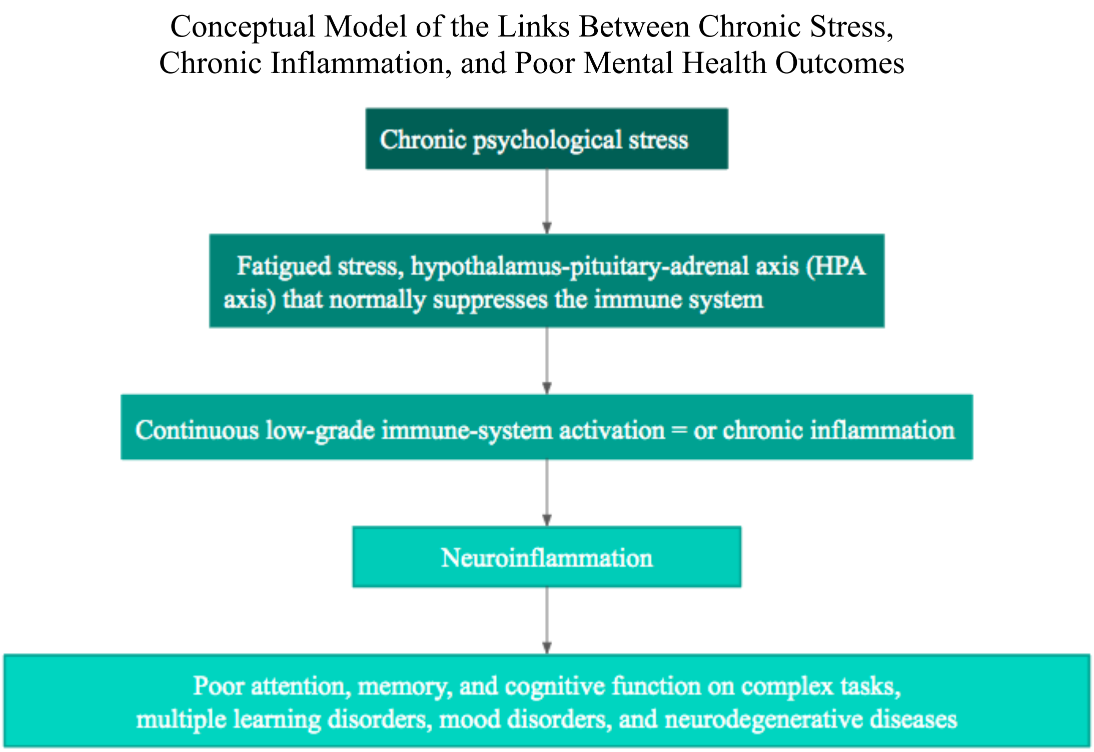

Figure 1: Schematic diagram depicting the links between chronic psychological stress, chronic inflammation, and low cognitive function as well as an elevated risk for mental disorders and diseases.

In contrast to acute stress, chronic psychological stress has a somewhat opposite effect on the immune system. Chronic stress stimulates the stress system to the point of lasting fatigue of the HPA axis (Starr et al., 2019). This fatigued HPA axis fails to suppress the immune system, which instead enters a state of continuous low-grade activation or chronic inflammation (Fig. 2; Gold et al., 1987; Karin et al., 2020), where acute inflammation is no longer followed by resolution/termination of inflammation and where levels of proinflammatory messengers such as cytokines remain elevated (Chen et al., 2018; Starr et al., 2019; Zhang and An, 2009) and prevent resolution of acute inflammation. Cytokines are also involved in the initiation and maintenance of pathological pain (Xie et al., 2006; Zhang and An, 2009). This state of non-resolving inflammation leads to self-attack on otherwise healthy tissues in the brain (causing neuroinflammation) (Dhabhar and McEwen, 1997, Dhabhar, 2009) as well as other organs (Stegerstrom and Miller, 2006), and simultaneously leads to poor immunity against pathogens and other invaders (Andersen et al., 2021; Mulder et al., 2009; Segerstrom and Miller, 2006). Whereas acute stress enhances components of the immune system and increases the numbers of natural killer (NK) cells and T cells (Dhabhar and McEwen, 1997), chronic non-resolving inflammation leads to low NK cells and T cell counts (Andersen et al., 2021; Mulder et al., 2009; Han et al., 2016; Segerstrom and Miller, 2006). NK cells are key members of the immune system (Andersen et al., 2021; Han et al., 2015; 2021 Lee, 2012) that kill tumor cells or virus-infected cells (Han et al., 2015; Lee, 2012). T cells also protect against infection (Kumar et al., 2018). Notably, increases in NK cells numbers are associated with other elements of a restored immune response, such as anti-inflammatory (Lee, 2012), anti-asthmatic (Chen et al., 2018; Lee, 2012), and anti-allergic health outcomes (Han et al., Kuo, 2015; 2015; Lee, 2012).

3. Literature Synthesis

3.1 Overview

This thesis offers a comprehensive synthesis of the literature on nature exposure as a means to combat chronic inflammation. Specifically, I synthesize and integrate the current literature through an analysis of nature-exposure-associated factors that influence immune health, including mediators (causal links) such as feelings of awe and improved mood, and link these responses to the support of nature exposure for cardiovascular relaxation and a health-promoting gut microbiome (microbiome eubiosis) (Figs. 2, 3).

Currently available interventions that lower the level of inflammation have been shown to increase cognitive function and lower the risk for disorders and diseases. Examples include Cognitive behavioral therapy (CBT) (Stigsdotter et al., 2018), mindfulness therapy (Turner et al.,

Overview of Mediators Between Nature Exposure and Positive Health Outcomes

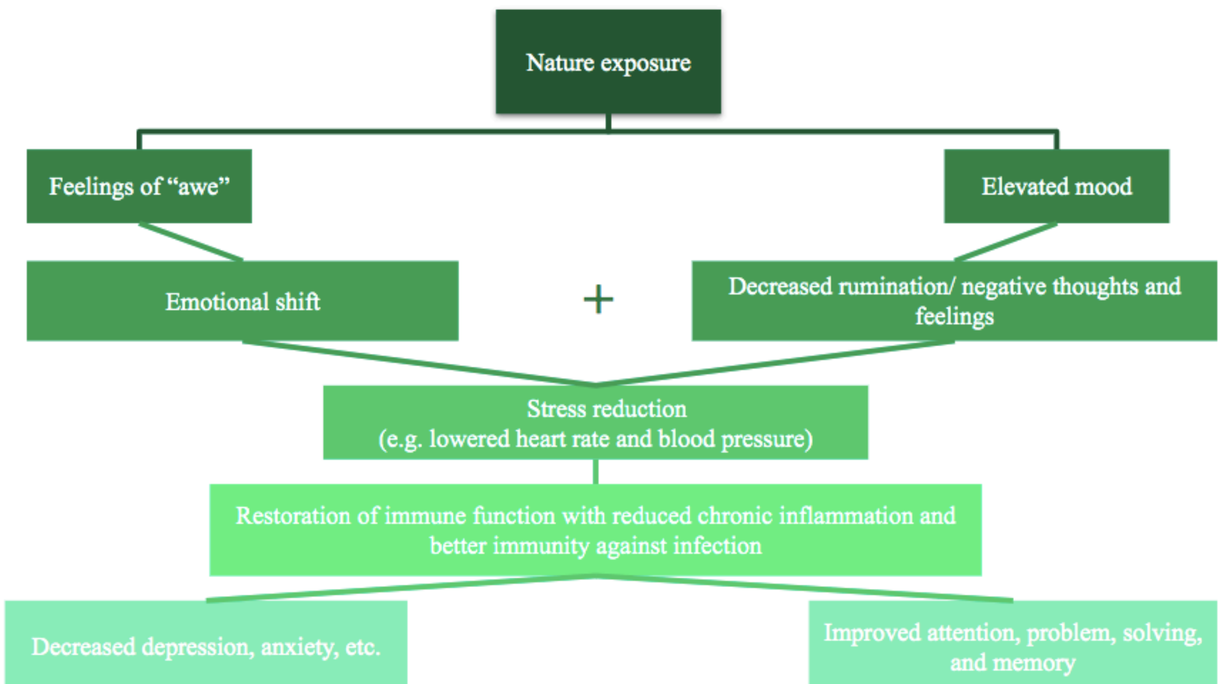

Figure 2: Overview of connections between nature exposure, mediators such as awe and improved mood (Chirico and Gaggioli, 2021; Lopes et al., 2020) and their effects on emotion, rumination (Lopes et al., 2020; Nolen-Hoeskema et al., 2008), stress reduction (Bratman et al., 2020; De Vries et al., 2013), and negative thoughts and feelings (Bratman et al., 2020) that have implications for our body's physiological response (Bhasin et al., 2013; Lee et al., 2012; Shuda et al., 2020; Song et al., 2016; Stigsdotter et al., 2018; Ulrich et al., 1991), immune function, mental health (Berry et al., 2009; Kuo, 2015; Lopes et al., 2020; Stigsdotter et al., 2018) and cognitive thinking (Kim et al., 2021; McMahan and Estes, 2014; Stigsdotter et al., 2018).

2020), yoga (Bhasin et al., 2013), etc. Throughout the following literature synthesis, I examine the role of feelings of awe and improved mood, and an associated decrease in negative rumination. These mediators provide links between natural environments and stress reduction as well as prevention/resolution of chronic inflammation. Moreover, as shown in Figure 3, I link modernization-included alterations such as climate change and control, urbanization, and social inequality to limitations in the availability of, and access to, natural environments and propose

Conceptual Model of Management Approaches Needed to Improve Access to Nature Exposure and Its Health Benefits

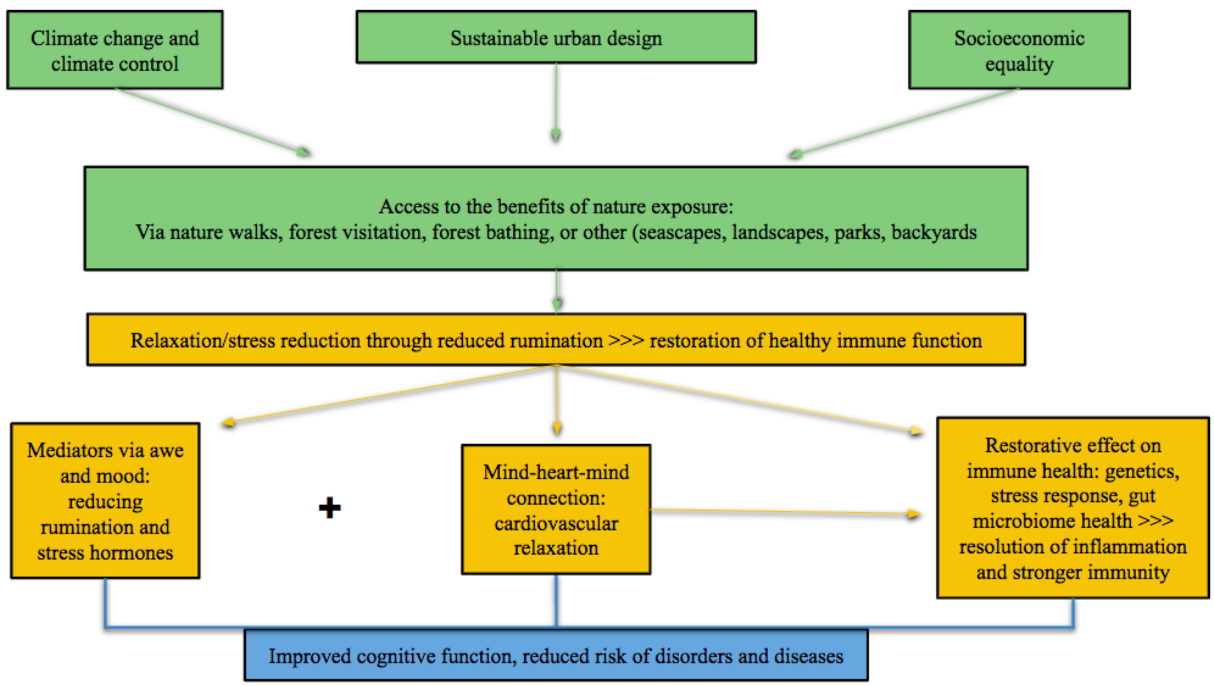

Figure 3: Schematic depiction of (i) policies required to preserve access to natural environments (green) and (ii) psychological and physiological mechanisms by which nature exposure restores immune function and other key functions required for cognitive function and health (blue).

climate control, sustainable urban design, and improved socioeconomic equality as necessary measures to improve access to nature exposure.

The following sections first visit each of the components shown in yellow in the conceptual model described in Figures 2 and 3. I then link these psychological and physiological effects to modernization-induced alterations in access to natural environments, shown in green. By doing so, this literature synthesis highlights the intertwined nature of mental and physical health (Berry et al., 2009; Bratman et al., 2020; Kemp and Quintana, 2013; Ohrnberger et al., 2017; Stigsdotter et al., 2018; Trostrup et al., 2019; Ulrich, 1984; White et al., 2019).

3.2 *Mediators between nature exposure and health benefits: awe and elevated mood*

Rumination is defined as obsessive thinking about a situation, choice, or idea, particularly when it interferes with normal cognitive functioning (Merriam-Webster; Nolen-Hoeksema, 1991). Such negative rumination can be reduced through a shift in attention away from oneself, particularly negative self-descriptive patterns of thought (Bratman et al., 2015; Hvenehaard et al., 2015; Lopes et al., 2020). Rumination is typically operationalized through a Ruminative Response Scale (RRS) self-report survey method, measuring ones' tendencies to use ruminative thinking when in a negative mood (Nolen-Hoeskema, 1987). Nature exposure can have a relaxing effect by providing positive neural distractions (Bratman et al., 2015; Lopes et al., 2020; Nolen-Hoeskema et al., 2008) and reducing stress (Lee et al., 2012), which can rapidly and unconsciously uplift mood (Figure 4; Bratman et al., 2015; Lopes et al., 2020; Ulrich et al., 1991) with positive implications for healthy immune function (Figs. 3 and 4; Andersen et al., 2021; Bhasin et al., 2013; Kim et al., 2020; Stoffel et al., 2020; Zhang and An, 2009). There must be a reset periodically to ones' chronic stress and ruminating thoughts to resolve inflammation in the body, rather than eliminating all stress to see results on immune functioning (Lee et al., 2012).

Such a shift in thought that elicits this periodic reset is associated with mood improvements in addition to the sensations of awe—as in wonder or amazement towards nature (Fig 4; Ketner et al., 2003, Lopes et al., 2020). Awe is an intense emotional response to perceptual stimuli that dramatically changes ones' understanding of the world. Common sources of awe include nature, music, art, and religious experiences, to name a few. It is operationalized through self-report survey and observational methods (Zhao et al., 2019). This direction away from rumination creates a pathway in which mood is improved through contact with nature (Bratman et al., 2015, Maller et al., 2006; Nolen-Hoeksema et al., 2008). There was found to be a significant correlation between the ratings of awe and the externally oriented thoughts ($p < 0.001$) (Lopes et al., 2020). The effect size of awe on negative thoughts using Cohen's d was found to be strong ($f = -0.84$). This indicates that awe directly decreases negative ruminating thoughts (Lopes et al., 2020). Both mediators (awe and mood) between nature and immune health reduce negative rumination (Figs. 3 and 4; Chirico and Gaggioli, 2021; Lopes et al., 2020, Nolen-Hoeksema et al., 2008) and the production of stress hormones (Lee et al., 2012; Segerstrom and Miller, 2004).

The following examples of nature exposure had measurable health benefits. The decreased scores of self-reported stress (Shuda et al., 2020) were seen as a result of 90-minute walks (Bratman et al., 2015), a group living in rural areas with greater green space versus city living (Roe et al., 2013), visiting outdoor parks versus a group with limited access (Shanahan et al., 2016), exposure to sounds from natural environments (Alvarsson et al., 2010), viewing pictures and sounds of nature on a videotape (Ulrich et al., 1991), increased tree exposure (Beyer et al., 2014), or gardening space in

Awe and Mood Elevation as Mediators of the Link Between Nature Exposure and Reduced Rumination

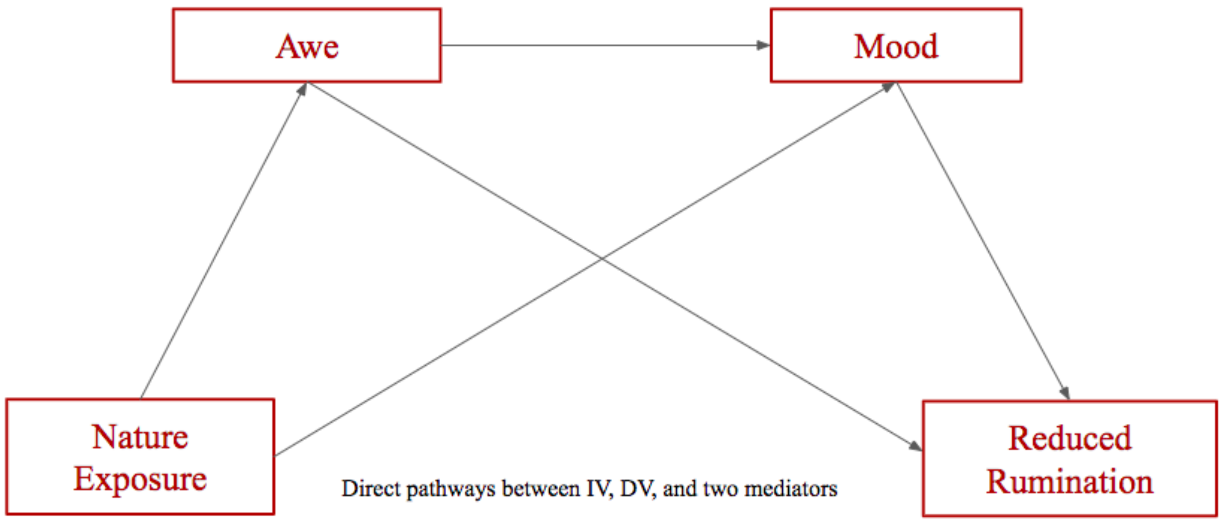

Figure 4: Schematic diagram depicting the relationship between two mediators, awe and mood, and their effects on a reduction in rumination, specifically negative feelings linked to depression, anxiety, and chronic stress. Nature exposure is the independent variable impacting both mediators and the dependent variable, rumination. (Modified from Lopes et al., 2020) In these models, any strong mediators (here awe and mood, respectively) typically make the direct link between cause (nature exposure) and outcome (rumination reduction) no longer statistically significant.

urbanized settings (Thomas et al., 2016). Specifically, human exposure to nature provoked an emotional response, such as feelings of awe, which focused attention on nature (Keltner and Haidt, 2003, Lopes et al., 2020) and triggered physiological responses to the sights, smells, exposure to natural light, and feelings (O'Malley, 2020; Turner et al., 2020). The response to nature exposure can thus be viewed as a feeling of connection and familiarity with specific places with natural experiences (Stigsdotter et al., 2018; Stoffel, et al., 2020). Signals detected by our senses (sight, sounds, smells, tastes) help create this connection with nature (Bratman et al., 2015; Bratman et al., 2020; Lopes et al., 2020; Ulrich et al., 1991) via the unconscious, bottom-up processes. Bottom-up processing is described as the retrieval of sensory information from our external environment to build perceptions on the current sensory information input (Gibson, 1972).

Time spent around trees and forests, gardens, parks, and green space (land partly or completely covered in grass, trees, or vegetation) (Taylor and Hochuli, 2017) is used in nature based therapies (NBT) (Annerstedt and Wahrborg, 2011; Corazon et al., 2010; Stigsdotter et al., 2018). NBT are therapeutic interventions that integrate natural elements including plants, natural materials, and outdoor environments, to treat psychological and physiological disorders (Corazon et al., 2010; Marcus and Barnes, 1999; Stigsdotter et al., 2018). NBT can induce the feeling of awe (Lopes et al., 2020) through nature activities, leading to a reduction in rumination (Bratman et al., 2015, Lopes et al., 2020, Marcus and Barnes, 1999).

A connection between mental and physical health is demonstrated by the high level of comorbidity between physical and mental diseases (Anderson, 2001; Groenewegen et al., 2012; Maas et al., 2009; Kuo, 2015). Patients in surgical wards with non-communicable diseases, such as cancer, who were able to view natural environments through their windows while under hospital care showed faster rehabilitation with reduced lengths of hospital stay, dosage of pain killer use, and fewer postsurgical complications compared to controls (Ulrich, 1984). Similarly, NBT in patients with severe stress-related illnesses resulted in a statistically significant self-reported increase in overall well-being of patients over time and decreased burnout scores (Lundgren-Nilsson et al., 2012; Stigsdotter et al., 2018). Nature interventions, such as prolonged periods of time in outdoor adventure programs (1-3 week programs), with cancer patients significantly reduced depression, increased self-esteem, body image, and reduced chronic stress compared to control groups (Buckley and Brough, 2017; Trostrup et al., 2019; Rosenberg et al., 2014). It has been proposed that the feeling of awe, where nature brings a sense of passive comfort, plays a role in all of these benefits by tapping into the ingrained human desire for safety and removal of discomfort (Bratman et al., 2012; Lopes et al., 2020). Notably, even a 30-minute walk in an urban park uplifted mood and reduced rumination compared to no such benefits in control participants who walked in a city (Lopes et al., 2020).

3.3 *Mind-heart-mind connection: Cardiovascular relaxation*

The mind-heart-mind connection (Fig. 5; Levine, 2019) is a reciprocal link between brain and cardiovascular health (Levine, 2019; Rieckmann et al., 2006). The heart communicates biochemically, energetically, and physiologically with the brain (McCraty, 2004). When we experience stress and negative emotions, the heart is affected through erratic disorganization of its electrical rhythm (Levine, 2019; McMahan and Estes, 2015; Pobachenko et al., 2006). Psychological distress or negative emotions cause an elevation of cardiac risk factor biomarkers (Levine, 2019; Lee et al., 2012; McMahan and Estes, 2014; Panksepp and Biven, 2012) that are related to high blood pressure (Berry et al., 2009; Lee et al., 2012; Levine, 2019; Mills et al., 1995), systemic inflammation (Andersen et al., 2021; Levine, 2019; Chen et al., 2018; Starr et al., 2019; Zhang and An, 2009), elevated cholesterol levels (Januzzi et al., 2000, Levine, 2019), obesity (Van Gaal et al., 2006), and more.

Stress reduction and reduced rumination (Bratman et al., 2015; De Vries et al., 2013; Lopes et al., 2020) acts, in part, through the mind-heart-mind connection (Fig. 4; Levine, 2019) and responds to cardiovascular relaxation methods, such as deep breathing (Peterfalvi et al., 2021), mindfulness practices (Turner et al., 2020), nature-based therapies (Annerstedt and Wahrborg, 2011; Corazon et al., 2010; Stigsdotter et al., 2018), etc., by inducing relaxation of the parasympathetic autonomic nervous system (Karin et al., 2020) that further lowers heart rate (Fig. 2; Dhabhar and McEwen, 1997, 2001; Stoffel et al., 2020). Stable patterns of the heart rhythm are reinforced through positive feelings and emotional stability (Ballew and Omoto, 2018; Bratman et al., 2019; de Vries et al., 2013; McMahan and Estes, 2015). In contrast, mental fatigue (Hypothesis

2; Ballew and Omoto, 2018, Hartig et al., 2009, Lee et al., 2009) increases hypertension (Berry et al., 2009; Mills et al., 1995), diabetes risk (Andersen et al., 2021; Dhabhar, 2009; White et al., 2019), obesity (Van Gaal et al., 2006; White et al., 2019), and cardiovascular risk factors (Dantzer et al., 2008, Dhabhar, 1998, 2009).

Increased relaxation of the cardiovascular system (Levine, 2019; McMahan and Estes, 2015) as a result of even short-term relaxation therapies (Pal et al., 2014), such as experiencing awe, provides a "psychotic break or psychedelic experience" (Keltner and Haidt, 2003; Chirico and Gaggioli, 2021). This experience induces relaxation (Chirico and Gaggioli, 2021; Levine, 2019; Rieckmann et al., 2006) and is describes a sudden transformation where a person feels intense emotions (Chirico et al., 2018) that trigger changes in parasympathetic and sympathetic activity (Fig. 2; Andersen et al., 2021; Karin et al., 2020; Myers, 2017; Song et al., 2016) and bring relief from negative rumination (Chirico et al., 2018; Chirico and Gaggioli, 2021; Silvia et al., 2015). Contact with nature is thus considered a reset from chronic stressors and fosters the above-described sense of relaxation and stress reduction (Lee et al., 2012; Peterfalvi et al., 2021), which also boosts immune function (Andersen et al., 2021; Dhabhar, 2009), improves sleep (Bhasin et al., 2013), and has other benefits such as reducing depression and anxiety (Januzzi et al., 2000; Levine, 2019), and increasing comfort (Bratman et al., 2015; Lee, 2012).

Restorative natural environments are used to help individuals recover from mental and physical fatigue (Fig. 2; Kaplan, 1995; Louati and Berenbaum, 2015; Maller et al., 2006; Nikolaus et al., 2013) as well as promote cardiovascular relaxation (Peterfalvi et al., 2021) and provide a setting for patients to remove themselves from the stressors of daily life (Maller et al., 2006, Ulrich et al., 1991). Whereas a psychologically fatigued state can send signals to the body to rest exhausted, overworked tissue (Fig. 2, Louati and Berenbaum, 2015; Nikolaus et al., 2013), resting or lying down does not provide relief (Lee et al., 2012; McMahan and Estes, 2015). In contrast, restorative environments reduce such psychological fatigue and nervous-system imbalances (Andersen et al., 2021, Myers, 2017; Song et al., 2016). Positive distractions and decreased rumination lower the fight-or-flight response by relaxing the stress response (Dhabhar and McEwen, 1997; Dhabhar, 2009; Maller et al., 2006; Stegerstrom and Miller, 2006).

Health promotion and decreased rumination (Andersen et al., 2021; Bratman et al., 2021; Chirico and Gaggioli, 2021; Peterfalvi et al., 2021; Shuda et al., 2020) were seen as a result of therapeutic approaches in restorative natural environments, such as walking and other forms of exercise outdoors (Bratman et al., 2015; Kaplan and Kaplan, 1989; Lopes et al., 2020), breathing in nature (Kim et al., 2020; Peterfalvi et al., 2021), observations of natural scenery (e.g. bird watching, plant walks, hiking/camping, wildlife tracking, etc.) (Maller et al., 2005; Shanahan et al., 2016; Ulrich, 1984; Ulrich et al., 1991), and forest bathing (Andersen et al., 2021; Kim et al., 2020; Kim et al., 2021; Li, 2010; Peterfalvi, 2021). Forest bathing is a Japanese nature therapy practice in which we achieve a state of mindfulness through breathing in the forest air and heightening our senses, suspending any judgments, and focusing on the present now (Antonelli et al., 2019). Moreover, forest therapy-based interventions bring a sense of advanced comfort and relaxation (Bratman et al., 2015; Lopes et al., 2020; Lee et al., 2011; Lee et al., 2012; Tsunetsugu et al., 2010) and lowered stress hormones (cortisol) levels (Lee et al., 2012; Mayoclinic, 2022), as well as restoring the balance of sympathetic and parasympathetic nervous system activity (Lee et al., 2011, 2012; Tsunetsugu et al., 2010) via lowered heart rate and blood pressure (Berry et al., 2009; Lee et al., 2012; Levine, 2019; Mills et al., 1995).

3.4 *Restorative effects on immune health*

Reduced rumination as a result of exposure to nature (Bratman et al., 2015, Lopes et al., 2020) also lessens chronic inflammation (Figs. 3 and 4; Chen et al., 2018; Chirico and Gaggioli, 2021; Zhang and An, 2009). These effects can involve the common rapid changes in gene expression and long-term activation or inactivation of genes via epigenetic effects (Fig 5; Deichmann, 2016; Meaney, 2010; Zhang and Meaney, 2010). Our environment impacts the expression of many genes. An example is the rise in blood sugar level after a meal that prompts insulin synthesis via increased expression of the insulin gene, which results in removal of sugar from the bloodstream into storage depots in liver and muscles (Wilcox, 2005). An example for an epigenetic effect is a constant activation by histone modification/DNA methylation of genes of appetite-stimulating hormones in the offspring of a mother who experienced food insecurity prior to or during pregnancy (Carmichael et al., 2007). Both short-term and lasting, long-term (epigenetic) modulations of gene expression influence the human stress response (Dhabhar et al., 1997; Dhabhar, 2009, Maller et al., 2006; Rook 2013; Stoffel et al., 2020), and thus the inflammatory response (Deichmann, 2016; Tarnowski et al., 2021) as a result of environmental stimuli (McCall et al., 2010) including lifestyle and environmental factors (Andersen, et al., 2021; McCall et al., 2010; Tarnowski et al., 2021). Both pro- and anti-inflammatory responses (such as Nk cell counts and cytokine levels (protein hormones) are modulated by changes in gene expression (Andersen et al., 2021; Han et al., 2015; 2021 Lee, 2012; Dhabhar, 2009).

The importance of the involvement of epigenetics lies in the potential of nature exposure to undo lasting adverse effects written (epigenetically) into our genes through prior exposure to stressful environments. Access to nature did affect epigenetic alterations of gene expression patterns (Andersen et al., 2021; Deichmann, 2016; Dhabhar, 2009; Han et al., Effects of Nature Exposure on Gene Expression, Stress Response, Microbiome, and Immune Health

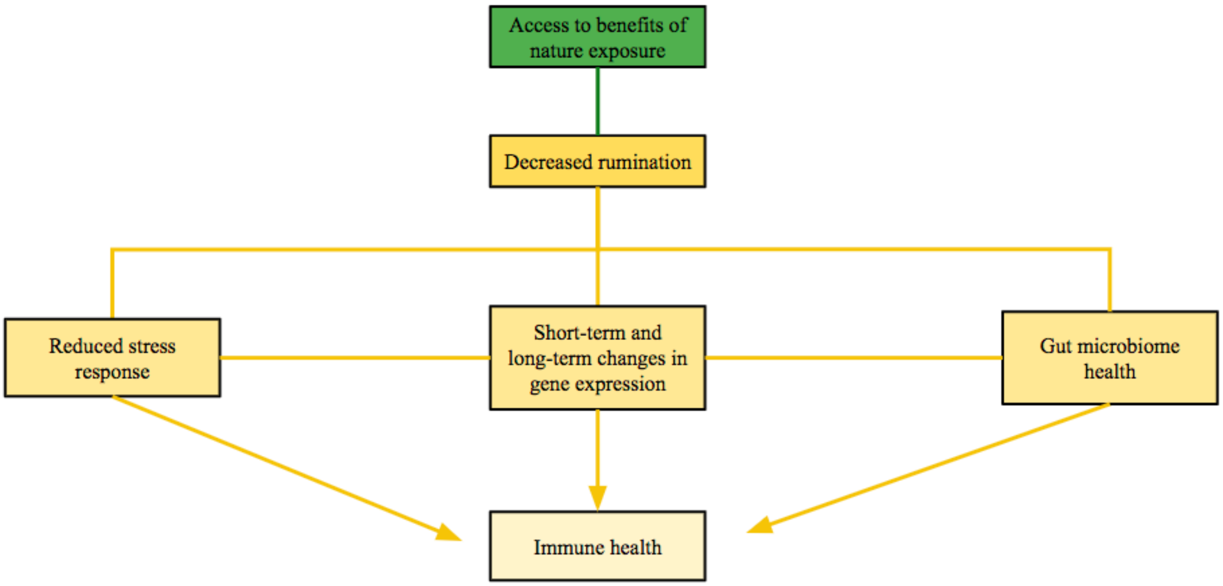

Figure 5: Schematic diagram illustrating facets that influence restorative effects of nature exposure on immune health.

2015; 2021 Lee, 2012), ameliorated prolonged stress (Lopes et al., 2020; Zoccola et al., 2014), and improved gut microbiome health (Iebba et al., 2016; Seirov et al., 2006) as three factors with implications for immune health and chronic inflammation.

Negative rumination does have a prolonged effect and causes stress-response imbalances and chronic inflammation (Lopes et al., 2020; Zoccola et al., 2014). Specifically, negative emotions are associated with sustained elevation of proinflammatory cytokines (Lopes et al., 2020; Stellar et al., 2015 (Said et al., 2020; Stellar et al., 2015, Zoccola et al., 2014), which can be associated with long-term epigenetic alterations of gene-expression patterns (Andersen et al., 2021; Dhabhar, 2009; Lee, 2012). Since negative mood and rumination reinforce each other (Lopes et al., 2020; Watkins and Mason, 2020) and are associated with poorer health outcomes (Kiecolt-Glaser et al., 2002; Stellar et al., 2020), interventions that stimulate feelings of awe can lower levels of proinflammatory cytokines (Figs. 1 and 2; Chen et al., 2018; Starr et al., 2019;

Zhang and An, 2009) and enhance well-being (Gordon et al., 2017; Lopes et al., 2020; Stellar et al., 2015). Reduction in rumination thus has the potential to lower chronic inflammation (Lopes et al., 2021; Bratman et al., 2015; Claesson et al., 2012; Rook, 2013; Stoffel et al., 2020) and self-attack on previously healthy tissues. Exposure to green space has been suggested to be key to enhancing stress recovery and management (Bratman et al., 2019; Fett et al., 2019; Groenewegen et al., 2012; van Herzele and Wiedemann et al., 2003; Roe et al., 2013), resetting epigenetic markers (Dhabhar et al., 1997; Dhabhar, 2009, Maller et al., 2006; Rook 2013; Stoffel et al., 2020), and restoring gut microbiome health (Iebba et al., 2016; Seirov et al., 2006) through the reduction in rumination and chronic proinflammatory responses in the heart, lungs, liver, kidneys, brain, etc. (Chen et al., 2018; Lopes et al., 2020).

A primary disadvantage to immune system dysfunction is poor immunity against invaders. Nature exposure is capable of reversing these adverse effects by, e.g., increasing NK cell counts (Andersen et al., 2021). For example, a two-day forest therapy program with patients with chronic pain reported increased immune response measured by NK cell activity and pre-and post-measured heart rate variability (HRV) associated with physiological improvements (Han et al., 2016). Participants in the forest-exposure group rather than the control group reported decreased pain and depression as well as improvements in overall quality-of-life (Han et al., 2016). In addition to an improve immune response, (Han et al., 2015; 2021 Lee, 2012), forest exposure also decreased chronic inflammation, presumably by shifting attention and emotional state to the environment (Han et al., 2016) and eliciting that feeling of awe (Chirico and Gaggioli, 2021; Lopes et al., 2020). Nature-induced rumination reduction can thus promote health in chronically ill patients (Han et al., 2016; Kuo, 2015).

Beyond the impacts on mood, forests provide air-borne compounds with anti-inflammatory properties (Peterfalvi et al., 2021) that may serve in holistic approaches to treating inflammatory diseases (Kim et al., 2020, 2021) that affect the respiratory system (Andersen et al., 2021; Frumkin et al., 2017), cardiovascular system (Kim et al., 2020; Frumkin et al., 2017; Rieckmann et al., 2006; White et al., 2019), and the brain (Kim et al., 2020). There is evidence that prolonged exposure to forest bathing and other interventions such as nature trips (Andersen et al., 2021; Corazon et al., 2010; Marcus et al., 1999) are safe therapeutic strategies for immune-function restoration (Pal et al., 2014; Rosenberg, 2014) and decreasing side effects from diseases affecting the respiratory system (Andersen et al., 2021; D'Amato and Cecchi, 2008; Pal et al., 2014). Spending time in environments with pines, oaks, and maple forests have particularly significant benefits in lowering chronic inflammation of the respiratory system (Andersen et al., 2021; Frumkin et al., 2017; Han et al., 2016) and promoting gut microbiome eubiosis (Andersen et al., 2021; Claesson et al., 2012; von Hertzen et al., 2011).

The gut microbiome is important for supporting immune function, and forest and nature interventions such as bathing, walking, and spending spare time in rural outdoor areas (Andersen et al., 2021; Iebba et al., 2016; Peterfalvi et al., 2021) can enhance microbiome eubiosis (Fig. 5, Andersen et al., 2021; Kamada et al., 2013). Microbiome eubiosis is considered as the microbial balance within the human body (Iebba et al., 2016). The number of microorganisms in and around our bodies is tenfold higher than our cell count (Iebba et al., 2016; Seirov et al., 2006). The gastrointestinal (GI) tract has a high population of microbiota (Iebba et al., 2016; Sartor, 2008). Taxa that sustain gut microbiome health include *Bacteroidetes, Proteobacteria, Verrucomicrobia, Actinobacteria, Bifidobacteria*, *and Fusobacteria* (Iebba et al., 2016; Sartor, 2008; Zoetendal et al., 2008). The gut microbiome plays a critical role in supporting a balanced immune response

(Kamada et al., 2013; Iebba et al., 2016; Sartor, 2008; Zoetendal et al., 2008), preventing autoimmune diseases (Littman and Rudensky, 2010), and protecting against pathogens and other harmful microorganisms (Iebba et al., 2016; Sekirov et al., 2010). The gut microbiome is heavily influenced by environmental factors (Iebba et al., 2016; Sartor, 2008).

The human microbiome is affected by the emotional state of the human host (Claesson et al., 2012), various aspects of the external environment (Mulder et al., 2009), contact with other humans and animals (Lee et al., 2012), and diet (Claesson et al., 2012). In addition to supporting existing human microbiomes, nature exposure can supply beneficial bacteria commonly found in soils, water, and air for incorporation (Mulder et al., 2009; von Hertzen et al., 2011). Bacteria from forest aerosols (Han et al., 2016; Iebba et al., 2015; von Hertzen et al., 2011) can protect the nervous system (Hooper et al., 2001; Stella et al., 2015) against imbalance due to chronic stress (Iebba et al., 2016; Starr et al., 2018), and resulting chronic inflammation (Karin et al., 2020; Iebba et al., 2016; Nobuuyuki et al., 2004).

By way of the gut-brain axis (Clapp, et al., 2017; Cryan et al., 2019), gut microbiome dysbiosis can contribute to mental illnesses such as anxiety, depression, and negative rumination (Januzzi et al., 2000; Levine, 2019). Natural probiotics from aerosols and soil exposure (Pahwa et al., 2018), in addition to those from the diet, support immune health (Andersen et al., 2021; Laothawornkitkul et al., 2009). Anxiety, depression, rumination (Lopes et al., 2020), and poor brain function are associated with deregulation of inflammatory messengers and neurotransmitters (Andersen et al., 2021; Dhabhar et al., 1993; Dhabhar, 2009), with elevated levels of pro-inflammatory cytokines (Said et al., 2020; Stellar et al., 2015, Zoccola et al., 2014). An example of a link between the gut microbiome and neurotransmitters is the modulation of gene expression for the receptor protein for gamma-aminobutyric acid (GABA), an amino acid that functions as a neurotransmitter in the central nervous system, by the absence or presence of *Bifidobacteria* species in the GI tract (Iebba et al., 2016; Kamada et al., 2013; Starr et al., 2018).

In addition to discouraging chronic inflammation (Haller, 2006), the human microbiome actively augments immunity against invaders (Andersen et al., 2021; Kurkjian et al., 2021). Moreover, exposure to a variety of external microorganisms in external natural environments (Iebba et al., 2016) trains the immune system in differentiating between wanted and unwanted cells (Iebba et al., 2016; Kamada et al., 2013) and in the resolution of acute inflammation when an attack has ended (Andersen et al., 2021). Decreased rumination (Bratman et al., 2015), elevated mood (Kamada et al., 2013; Lopes et al., 2020), and exposure to beneficial microorganisms through restorative environments can thus all improve microbiome eubiosis and restore a balanced function of the stress and immune systems (Claesson et al., 2012; Iebba et al., 2016; Sartor, 2008).

Mediation through awe and improved mood, and the mind-heart connection by means of cardiovascular relaxation through reduced rumination, work together to positively impact the chronic stress responses and help the restorative effects on immune health (Fig. 5). Better immune health lessens chronic inflammation and provides stronger immunity through stress reduction, relaxation, gene-environment interactions, and microbiome eubiosis (Fig, 5 yellow section).

Necessary Large-Scale Changes to Improve Access to Natural Systems

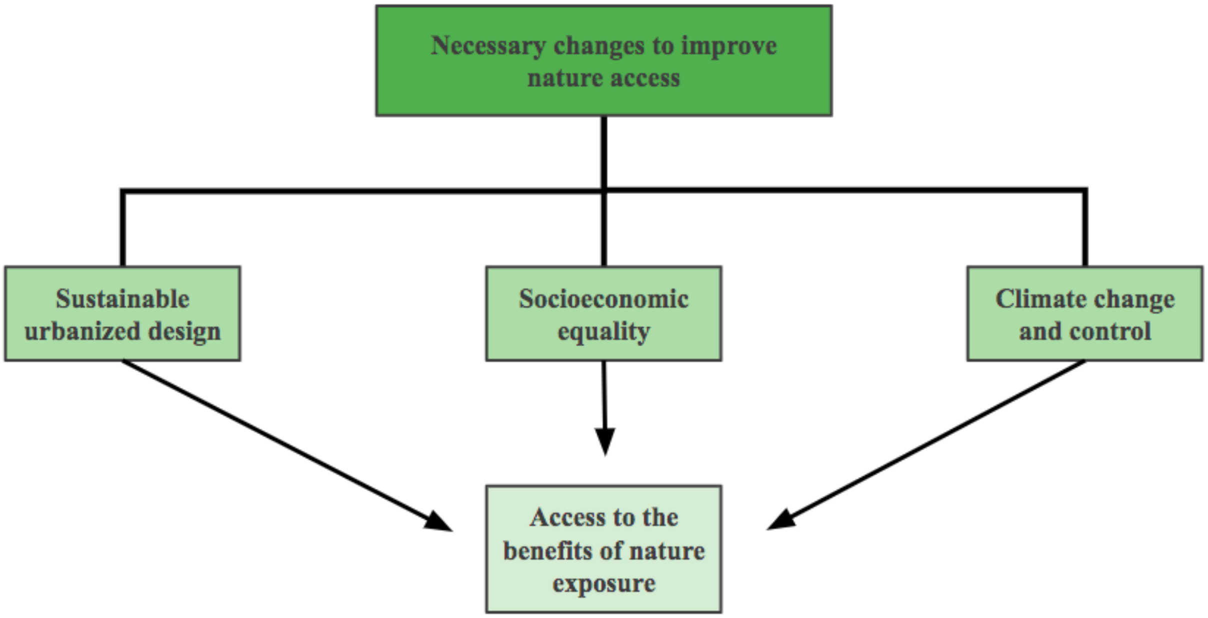

Figure 6: Schematic diagram illustrating necessary changes to improve access to natural systems. Sustainable urbanized design, socioeconomic equality, and climate control are needed to increase access to natural resources and greenspace (Bratman et al., 2019; Fett et al., 2019; Groenewegen et al., 2012; van Herzele and Wiedemann et al., 2003; Roe et al., 2013).

3.5 *Sustainable urbanized design*

Quantity and quality of greenspace are important indicators of health benefits (Fig 4; Bratman et al., 2019; de Vries et al., 2013; Kahn Jr., 2002). There is a positive relationship between time spent in nature and cognitive function (Aspinall et al., 2015; Dhabhar, 2009), decreased chronic stress (Ulrich et al., 1991; Hartig et al., 2003; Roe et al., 2013), lower blood pressure, hypertension (Lee et al., 2012; Peterfalvi et al., 2021; Roe et al., 2020), decreased chronic inflammation (Rook, 2013) and associated non-communicable diseases (Andersen et al., 2021; Bratman et al., 2019; de Vries et al., 2013; Maller et al., 2005). The quality of green space is associated with the attractiveness of landscapes (Bratman et al., 2019; Fett et al., 2019; van Herzele and Wiedemann et al., 2003) and can directly influence walking and exercising behavior (Sugiyama et al., 2008). Walking or other forms of exercise in parks and forests satisfy four main elements to decreasing stress: (i) fascination, a form of attention that hones in on human curiosity; (ii) sensation of being away from stressor, described as a temporary escape from reality (Cawte, 1967; Kaplan and Kaplan, 1989); (iii) extent of experience, described as being a part of a larger whole than a small scope of everyday interactions; (iv) individual inclination, expressed as the opportunity to feel purpose as an individual (Kaplan and Kaplan, 1989; Sacks; 1987; Ulrich, 1979). These elements are manifestations of the feeling of wonder and amazement by nature through that feeling of awe (Lopes et al., 2020). This reconstruction and transformation, both conscious and unconscious (Keltner and Haidt, 2003; Pearsall, 2007; Chirico et al., 2018), of an individual mental frame through exposure to nature is what is considered therapeutic for mental health issues (Chirico and Gaggioli, 2021; Shiota et al., 2017).

Natural environments increase psychological restoration compared to urbanized, densely compact settings by improving the ability to recover from low mood (Fig. 6; Astell-Burt et al., 2014; Bratman et al., 2019; Lopes et al., 2020), negative rumination (Bratman et al., 2015), stress, and mental fatigue (Ballew and Omoto, 2018, Hartig et al., 2009; Lee et al., 2009; Neale et al., 2021). With over 55% of the world population living in urban areas (United Nations DoE, 2018) and the rise of urbanization due to over-population and crowding (Bratman et al., 2019; Khan, 2002), there is a lack of adequate green space or proximity to natural environments (Fett et al., 2019; Kirkbride et al., 2018). This trend appears to continue with the proportions of artificial (Song et al., 2016) and urbanized areas expected to increase to 70% by 2050 (Bratman et al., 2015; Dye, 2008).

Urban stress, exposure to environmental toxins from pollutants, and disease agents are associated with increased risk of elevated risks of psychosis and mental illness (Bratman et al., 2015; Fett et al., 2019; Lederbogen et al., 2011; Peen et al., 2010). Understanding urban risk factors is vital to sustainable urbanized design (Attademo and Bernardini, 2017) that can mitigate risk factors (Fett et al., 2019; Selten et al., 2007). Sustainable urbanized design is described as a relationship between the natural environment and urban structures. It encourages the revitalization of urban areas to increase livability and decrease environmental impacts, all while maximizing social benefits (Roggema, 2016). As stated above, available green space in urban settings may reduce risks for psychological disorders through decreased negative rumination (Bratman et al., 2015; Lopes et al., 2020) and the associated stress reduction (Bratman et al., 2020; De Vries et al., 201) as well as a lessening of exposure to pollutants (Engemann et al., 2018).

The positive effect of restorative areas (Ulrich et al., 1991) constitute psychological ecosystem services (Bratman et al., 2019; Hartig et al., 2014; White et al., 2017). It has been proposed (Brich, 1993; Maller et al., 2006) to incorporate these health-promotion agencies into policy decisions regarding public natural spaces in densely populated communities with decreased exposure to nature (Bowler et al., 2010; Bratman et al., 2019; Schwarz et al., 2015). Such policies would utilize public resources to fund restorative gardens and public natural spaces to benefit mental, social, environmental, and economic outcomes (Brown, 1995; Maller et al., 2005). (Bratman et al., 2019; Hartig et al., 2016; Frumkin et al., 2017; Van den Berg, 2017).

Psychological health is improved by proximity to green space (Bratman et al., 2019; Roe et al., 2013; Wheeler et al., 2015) and private gardens in urban settings (Dadvand et al., 2016; Mitchell et al., 2015; van den Berg et al., 2016). Spending time walking in parks provides restoration compared to walking in an urbanized city setting (Maller et al., 2005; Trapnell and Campbell, 1999; Bratman et al., 2015).

3.6 *Socioeconomic equality*

Green spaces in urban environments are particularly limited in economically disadvantaged areas, restricting the benefits of nature exposure to specific groups not only nationally, but also globally (Bratman et al., 2019; Schwarz et al., 2015). Environmental-justice advocates, academics, and policymakers recognize the disproportionality between burdens of environmental hazards and accessibility of nature in low-income and minority communities nationally and globally (Low et al., 2005; Schwarz et al., 2015). Low socioeconomic status (SES) is generally associated with an increased prevalence of mental health problems, health-impaired behaviors related to stress (Baum et al., 2006), and associations with higher risks for chronic inflammatory diseases (Louati and Berenbaum, 2015; Wolfe et al., 1996). Conversely, those with higher SES have more access to aesthetic and clean natural environments (Schwarz et al., 2015) than those with low SES (Kavanagh et al., 2005). Higher rates of morbidity and mortality are seen in individuals surrounded by less green space even after controlling for SES, gender, and ethnicity (Berry et al., 2009; Schwarz et al., 2015). Environmental equality is required to lessen the disproportionate burdens related to adverse health outcomes for racial and ethnic minorities in low income and disadvantages areas (Boone, 2008, Low et al., 2005; Schwarz et al., 2015) who often also have unequal access to healthful food (Cutts et al., 2009) parks, forests, open spaces, and gardens (Low et al., 2005; Pedlowski et al., 2002; Schwarz et al., 2015).

The available green space often varies by city size (Maller et al., 2005; Roggema, 2016), geographic location (Bratman et al., 2019; Schwarz et al., 2015), urban ecology (Low et al., 2005; Roggema, 2016), available geographic space, and presence of vegetation (Neale et al., 2021). For example, the Urban Tree Canopy (UTC) assessment, supported by the U.S Department of Agriculture, provides a measure of a community's tree canopy cover, and is working in urban cities such as Detroit, Los Angeles, New York, and Chicago (Schwarz et al., 2015). The UTC is often used for broader goals focusing on regulation of regional climate and water cycles as well as vegetation availability with the goal to reduce obesity rates (Van Gaal et al., 2006). However, more focus is needed on psychological ecosystem services to improve mental health in low-income populations (Baum et al., 2006). Economic and environmental deprivation in minority and low-income communities is considered a large risk factor for psychiatric disorders within cities (Kirkbride et al., 2017; Richardson et al., 2018; Fett et al., 2019) and mental health varies with SES, residential location, occupation, and culture (Astell-Burt et al., 2013; Bratman et al., 2019). Natural resources thus need to be made available to all communities (Baum et al., 2006) to counteract the trend of increasing concentration of populations in urban areas and resulting unavailability of nature experiences (Bratman et al., 2019; Khan, 2002). Currently, the unequal distribution of population density (Baum et al., 2006) severely limits the health benefits of awe and improved mood for populations of lower SES (Delahanty et al., 1998; Esterling et al., 1994; Lopes et al., 2020; Segerstrom and Miller, 2004).

3.7 *Climate Control*

The current environmental crisis results from concurrent effects of rapidly growing human populations on pollution (Fritze et al., 2008; Spickett et al., 2008), environmental degradation (Fritze et al., 2008; McMichael et al., 2008), contamination of soil, water, air (Mulder et al., 2009), and degradation of natural ecosystems across the globe (Andersen et al., 2021; Rook, 2013). Access to natural environments is thus decreasing due to population growth, urbanization, and destruction of natural environments associated with climate change (Thoma et al., 2021). Overcrowding has driven a disengagement from nature due to lack of availability and is causing “environmental generational amnesia” (Soga and Gaston, 2016) and “extinction of experience”

(Miller; 2005) that is likely to increase with each coming generation (Bratman et al., 2019; Khan, 2002).

The extinction of environmental experiences is driven by loss of the human-nature connection (Gaston and Soga, 2020; Miller, 2005) resulting in decreased sensory, visual, and acoustic interactions with organisms and restorative green space (Gaston and Soga, 2020; Miller, 2005; Nabhan and Antoine, 1993). This reduction in the emotional connection with nature (Soga and Gaston, 2016) also decreases pro-environmental attitudes and behaviors, creating a cycle of disaffection toward natural environments (Pyle, 1993; Soga and Gaston, 2016) and environmental accessibility (Gaston and Soga, 2020; Soga and Gaston, 2016).

Human-induced climate change is a reality for current and future generations around the world (Bratman et al., 2019; Miller, 2005; Soga and Gaston, 2016) with extreme heat, changes in patterns of infectious diseases (McMichael et al., 2008), limiting freshwater supply (Maller et al., 2005), and loss of livelihoods particularly for the most vulnerable populations. Continuation of the degradation trends seen today will have irreversible consequences for earth's life support system for human society (McMichael et al., 2008). The lack of a population-based focus or desire to make a change is the biggest threat to humanity's future (Fritze et al., 2008; Song, et al., 2016). Human attachment is a result of evolution and inherited adaptations (Stigsdotter et al., 2018; Stoffel et al., 2020) that tie stress, immune, and cardiovascular system as well as mental and physical health to exposure to natural environments (Soga and Gaston, 2016; Wilson, 1993). The relief, relaxation, restoration, and improved health and well-being as a result of nature exposure are presumably a direct consequence of human evolution in such settings (Andersen et al., 2021; Kellert, 2002; Tattersall, 2001; Song et al., 2016; Wilson, 1993).

As stated above, vulnerable people and places will be most adversely affected by the degradation of the natural environment (Berry et al., 2009). Human-induced climate change has implications for disease outcomes through warming temperatures (Fritze et al., 2008; Riberio et al., 2019) that enhance spread and prevalence of diseases, such as COVID-19 (Berry et al., 2009; D'Amato and Cecchi, 2008; Doherty and Clayton, 2011), and preventative measures are needed to slow environmental degradation and the associated negative outcomes for human health (Berry et al., 2009; Fritze et al., 2008; World Health Organization; 2005).

Natural resources need to be available and accessible to support interventions based on nature exposure (Andersen et al., 2021). Furthermore, decision-making efforts need to be shifted to focus on earth's "life-support system" for humans (Muhar et al., 2012) rather than merely services linked to biophysical dimensions (Bratman et al., 2019; Muhar et al., 2012).
Psychological ecosystem services are described as a positive mental health outcome resulting from an engagement with nature (Bratman et al., 2019), with psychological and ecosystem services (Bratman et al., 2019) used to lessen chronic stress and chronic inflammation. (Andersen et al., 2021; Hansen et al., 2016). Mental health benefits from experiencing nature therefore need to be incorporated into ecosystem services in future policy (Bratman et al., 2019; Hartig et al., 2014; White et al., 2017).

Enlightened self-interest may change attitudes and promote outdoor activities outdoors and increase available urban green space and nature visits, particularly amongst younger generations (Bratman et al., 2019; Roe and Aspinall, 2011) to enhance emotional affinity towards nature. It is encouraging that emotional connectedness with nature can be fostered even without regular interactions; a few days outdoors or a 30-minute walk (Lopes et al., 2020) can affect behavioral changes (Bratman et al., 2019). Continued promotion of pro-environmental behaviors (Collado et al., 2013) is needed to increase environmentally friendly behaviors and actions and their health benefits (Soga and Gaston, 2016; Wells and Lekies, 2006).

4. Conclusions and Recommendations

4.1 Evaluation of Hypotheses Tested

This literature synthesis supports both hypotheses formulated in Section 1.

(i) Access to restorative natural environments is associated with decreased chronic inflammation. In contrast to acute short-term stress, chronic stress due to lifestyle factors, diseases, and other challenges without a clear end point, causes dysregulation of the stress-response system. Chronic stress also causes the immune system to self-attack on the body and brain tissue, resulting in poor immunity, neuroinflammation, and impaired attention, memory, and cognitive function.

(ii) Nature exposure is linked to stress reduction and prevention of chronic inflammation through multiple mechanistic pathways. Specifically, contact with nature elicits a feeling of awe, shifting attention away from negative ruminating thoughts. As little as 30 minutes of walking in non-city environments can uplift mood. Both awe and elevated mood are mediators of the link between nature exposure and reduced negative rumination. Recreational nature contact can thus improve health and well-being and lower the risk for cardiovascular disease, obesity, diabetes, asthma, cancers, and mental distress. In addition to reduction of chronic psychological stress through awe and mood, nature exposure works through the mind-heart connection through cardiovascular relaxation.

4.2 *Implications and Policy Recommendations*

Climate change and increased human population density are reducing nature access and leading to a detrimental cycle of loss of natural connectedness, illness, and lack of interest in the conservation of natural environments. Restoration of natural environments is needed to support psychological ecosystem services, in particular to enhance the benefits of connectedness to nature in order to support mental function, which may then result in lowering the risk of multiple mental and physical diseases.

A focus on psychological ecosystem services is needed to bring together policy makers, city planners, educational professionals, researchers, and local citizens to contribute to climate-control efforts as well as preservation and restoration of natural environments. Specific recommendations include socio-ecological approaches to public health that emphasize the benefits of restorative environments for mental and physical health and engagement with psychological and environmental organizations at local, national, and global levels. This includes, but is not limited to: increasing education through media, community projects, and nature contact for younger generations to raise public awareness.

4.3 *Limitations*

This literature synthesizes integrated emerging insight from various disciplines, and future research in each of these areas may lead to a need for updates in the conclusions of this review. A main limitation of currently available research is a poor ability to differentiate the effects of lacking nature exposure in urban contexts from other effects of low SES, racial prejudice, and demographics (age, gender, culture) as well as regional geographic differences (Bratman et al., 2019; Schwarz et al., 2015). Moreover, whereas chronic inflammation is viewed here through the lens of chronic psychological stress, additional external factors (such as diet, physical activity level, and toxin exposure) also affect inflammation. In addition, there may be some level of internal bias in this review that focused on studies reporting benefits from nature exposure, with limited exploration of potential adverse effects. In addition, there is also a body of evidence for mental-health benefits of nature that do not discuss the mind-body connection.

This study also did not focus on specific age or other demographic or geographic groups and instead used a wide array of sample evidence across such groups from all over the world. Possible variation in the effect of nature exposure on health across the globe would not have been captured by this approach. Moreover, there was internal bias, specifically for the studies that were searched for and used that demonstrated only the health benefits of nature exposure. There does appear to also be publication bias in favor of looking for benefits rather than no effect on negative outcomes of nature exposure on human health.

Not all people may respond positively to nature exposure; some people may feel safer in cities than in nature. Individuals who grew up in environments with a lack of nature exposure may be more comfortable with urbanized spaces.

Nevertheless, there was a large amount of strong evidence to support that nature exposure has beneficial effects on human health and that many of these can be linked to positive effects on the immune system.

4.4 *Future Research*

Future research should explore physical- and mental-health effects of nature exposure, along with the impact of the lack of access to nature experiences, in a wider range of population groups, perhaps stratified by demographics, geographical locations, and racial, ethnic and cultural differences. Additionally, the emerging role of awe and elevated mood in conscious and unconscious feelings of wonder and amazement in a wide range of contexts should receive further attention. Similarly, the phenomenon of environmental extinction experience should receive further attention to elucidate whether decreasing human-nature interactions are due to lack of available natural resources, increased remoteness and online experiences, or a mixture of both. Although there is ample evidence for a link between general stress-reduction therapies and reduced chronic inflammation, specific links between reduced rumination and prevention of chronic inflammation need to be studied more extensively, rather than inferred as done here largely by synthesis of separate studies.

Moreover, there should be future research to investigate the roles of modern stressors related to continuous access to, and stimulation by, technology that may provide more constant, low-grade stress prior to modernization. Research should include the difference between low-grade, continuous stress and low-grade, continuous activation of the immune system as a possible phenomenon in modern times. What matters may not be the frequency and intensity of stress but whether or not there is any resetting in-between stressful events.

The conclusions of this literature synthesis can also be used to formulate additional specific hypotheses for future research based on the various associations and linkages identified here between natural environments and decreased chronic inflammation, stress reduction and prevention of chronic inflammation. Future research should address a wide variety of other reported effects of nature exposure that may also be directly or indirectly linked to reduced stress and inflammation. For example, various other activities and experiences associated with nature exposure may also produce feelings of awe and elevated mood as mediators and/or relaxation, reduced stress, and reduced inflammation as outcomes. Additional experiences that may elicit these reactions include:

(1) Enhanced creativity as a result of plant walks, wildlife tracking, bird watching, and/or observations of nature (Gladwell et al., 2013; Santana and Garcia-Mijares, 2022): One can hypothesize that nature exposure makes a contribution to getting people outdoors and moving and engaging in physical activity. Regular moderate physical activity can restore immune-system

function and the gut environment (Enichen et al., 2022). Promotion of physical activity through outdoors activities should thus reduce non-resolving inflammation.

(2) Improved performance and energy in the workplace through plant exposure: Flowers have been found (from self-reported surveys) to generate feelings of happiness when kept in the workplace, homes, and hospitals (Brethour 2007; Collins, 2008). Exposure to plants in indoor environments may thus help relaxation and improve mood, linking to the speed and performance of the completion of tasks (Bernstein, et al., 2009). An involvement of reduced chronic inflammation, especially neuroinflammation, in these effects should be assessed,

(3) Improvements in learning, attention, and engagement were seen in children who spend time around plants (Frank, 2003; Kellert, 2002). Teaching children at some young age the importance of whole, natural foods may also promote a balanced diet that is known to reduce chronic inflammation and restore the gut environment, e.g., through consumption of the many anti-inflammatory plant chemicals in vegetables, fruits, herbs, and spices (Adams et al., 2016). A balanced diet provides essential antioxidants that oppose pro-inflammatory signals and neuroinflammation (Polutchko et al., 2021). Promotion of a healthy diet at a young age may be particularly important for the prevention of obesity (Goldthrope et al., 2018), enhancing the human-nature connection, and supporting greater engagement, attention, and learning (Gaston and Soga, 2020).

(4) The benefits of conservatories in major cities such as the Amazon Spheres seen in Seattle, Washington (Coutts and Hahn, 2015) may be linked to feelings of awe and mood elevation. Exposure to botanical gardens and conservatories in urban areas may provide relief from negative rumination and provide a sense of safety and security (Raskin et al., 2002). Botanical conservatories also support vascular plant species that face extinction (Chen and Sun, 2018).

(5) Studies of neighborhood crime suggest that neighborhoods with more parks have lower crime rates (Austin, 2002). Nature exposure may reduce community crime through links between crime, low mood, aggression, and neuroinflammation (Wolfe and Mennis, 2012).

(6) Lastly, nature exposure has been shown to improve performance (Bernstein et al., 2009). Because there is also evidence for a link between stress/rumination and poor sleep and poor performance (Alotaibi et al., 2020), future research should assess a possible effect of these natural exposures in reducing neuroinflammation. An involvement of neuroinflammation has already been linked to poor memory, sleep, attention, and processing speed for the completion of tasks (Polutchko et al., 2021).

Future research should examine the linkages suggested in 1-5 above through a combination of methods that assess awe/mood, the ability to focus on the present surroundings rather than ruminate, and biochemical markers of underlying physiological changes from saliva and blood samples.

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